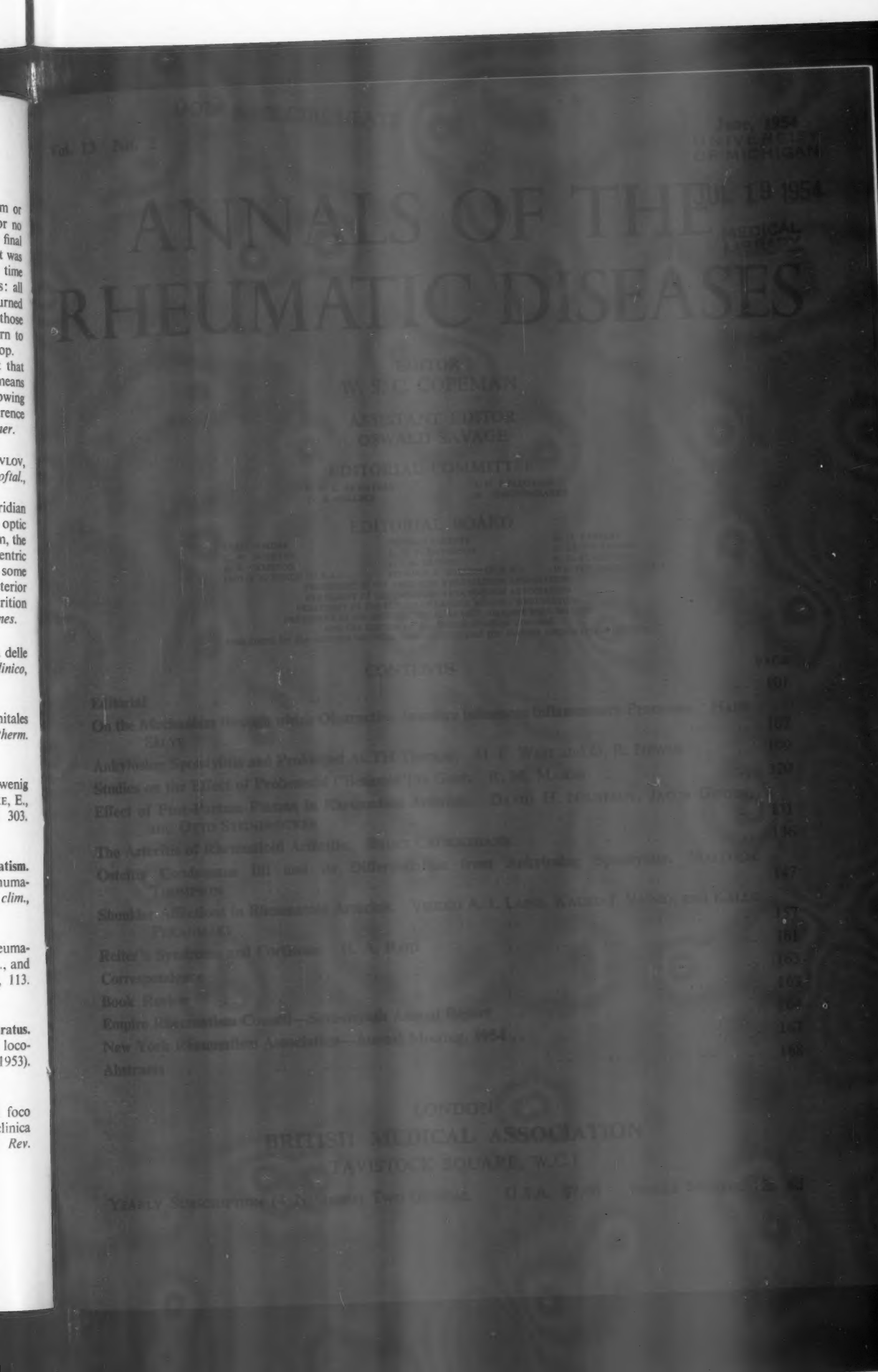

EDITORIAL

It is with the greatest pleasure that we are able to announce that Professor Walter Bauer of Boston, Massachusetts, has consented to join the Editorial Board of the *Annals*. Professor Bauer is well known to most rheumatologists, and his brilliant mind and critical erudition will be of immense value in the service of this journal.

Readers will no doubt have perused the recently published Report (1) of the Joint Committee of the Medical Research Council and Nuffield Foundation on clinical trials of cortisone, ACTH, and other therapeutic measures in the chronic rheumatic diseases. This describes two comparable groups of early cases of rheumatoid arthritis, one of which was allocated at random to treatment with cortisone and the other to treatment with aspirin. The assessment made at the end of one year records that the haemoglobin levels and erythrocyte sedimentation rates were slightly more favourably influenced by cortisone, but that the two groups differed materially in no other respect.

We have received letters from several correspondents pointing out that this depressing conclusion would appear to be at variance with that published (2) two weeks previously by a group of workers, some of whom were also signatories to the M.R.C.-Nuffield report. This latter group, however, approached the problem from a rather different angle, as all their patients were highly selected, and were severe cases of more than $2\frac{1}{2}$ years' standing, who described themselves as "crippled", and had failed to respond to all previous treatment. This series was followed up for as long as 3 years in some instances (all for over a year) and seventeen of the twenty patients were able, as the result of long-term cortisone therapy, to return to their occupations and are still able to remain at work.

We have no doubt that the apparent contradiction between these two series can be reconciled if the types of case used, the method of selection, and the technical details of the courses of treatment given are carefully studied. It would seem premature to assume from the results of the former, as the lay press in Great Britain seems to have done, that the era of cortisone is over.

If medical interest is to be maintained in the use of the steroid hormones in this field, any advance in chemical technique whereby the qualitative or quantitative assay of the products of adrenal activity can be rendered simpler and more accurate deserves notice. Dr. J. K. Norymberski, an Empire Rheumatism Council Research Fellow, working with a team of chemists in the University of Sheffield, reported at a recent meeting of the Biochemical Society (3), an interesting simple method for the estimation of the total urinary 17-hydroxy-corticosteroids, which may become a routine procedure for the estimation of the adrenocortical output of cortisol (hydro-cortisone 'free alcohol'), except when adrenocortical dysfunction is suspected. He has also shown that it is possible to assay selectively 17-hydroxy-20-oxosteroids. Steroids with the 17-hydroxy-20-oxo side-chain occur in the urine of patients with adrenal dysfunction; the late Konrad Dobriner of New York isolated such a steroid (17-hydroxy-pregnanolone) from the urine of six patients with rheumatoid arthritis, but found it to be absent from the urine of 28 normal persons, and suggested that there might therefore be some adrenal dysfunction present in this disease. It will be interesting to see whether the application of Norymberski's assay can throw further light on this important problem.

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Several inquiries have been received from Medical Schools and University Libraries abroad for back numbers of the *Annals*, especially those published between 1939 and 1945. It would be much appreciated if duplicate or unwanted copies could be returned to the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1, for redistribution to subscribers who wish to make up complete sets of the Journal. The cost of carriage will, of course, be refunded to those who are kind enough to co-operate in this way.

ON THE MECHANISM THROUGH WHICH OBSTRUCTIVE JAUNDICE INFLUENCES INFLAMMATORY PROCESSES*

BY

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A variety of experiments on animals had shown that the antiphlogistic effect of systemic stress is largely non-specific, in that it can be elicited by various agents and is effective in suppressing inflammation in various sites. For instance, systemic stress induced by diverse procedures, if it is sufficiently severe to elicit an intense general adaptation syndrome, markedly inhibits the so-called "histamine appendicitis" (Selye, 1936, 1937a), different varieties of acute inflammatory lung-oedema (Selye, 1938a, 1938b), and the anaphylactoid inflammation caused by egg-white in the rat (Selye, 1937b; Léger, 1948). Subsequently, it became evident that—at least under certain "conditioning" circumstances—systemic stress can also facilitate the production of inflammatory lesions (*e.g.* nephritis and myocarditis after exposure to cold). The adrenals were suspected of playing an important part both in the inhibition and in the enhancement of inflammatory phenomena by stress, since they were found to be greatly enlarged during the general adaptation syndrome, and since both the anti- and the prophlogistic effects of stress could be prevented by adrenalectomy (Selye, 1937b, 1946).

When pure corticoids became available, it was noted that some, the "mineralo-corticoids", are also "prophlogistic corticoids" (*e.g.* desoxycorticosterone) in that they stimulate, while others, the "gluco-corticoids", are also "antiphlogistic corticoids" (*e.g.* cortisone or cortisol) in that they inhibit inflammation (Selye, 1949; Selye and Pentz, 1943). However, the effects of endogenous cortical hormones upon inflammation are not solely dependent upon the rate of their production; the activity of these corticoids can be considerably modified by a variety of "conditioning factors" (Engel, 1953; Selye, 1954). The liver had long been suspected of playing an important role in this connexion. In the course of studies on the mechanism of this conditioning, we came to examine the influence of various experimentally induced hepatic injuries (partial hepatectomy, ligature of the common bile-duct) upon the actions of desoxycorticosterone, the first corticoid to be made available by synthesis (Selye, 1941, 1943; Selye and Stone, 1944). It was found that the effectiveness of this and many allied steroids can be strikingly enhanced by partial removal of hepatic tissue.

Independently, clinical experience had shown that, in patients with hepatic damage, inflammatory processes, and, in particular, rheumatoid lesions, tend to regress. The question arose whether this beneficial effect is merely due to an increased endogenous production of ACTH and of antiphlogistic corticoids —due to the systemic stress caused by the hepatic damage—or whether the liver is also more specifically involved in conditioning the efficacy of the corticoids after they are discharged into the blood. We were especially interested in clarifying this point, because of its practical importance. At present one of the greatest handicaps in the clinical use of antiphlogistic corticoids (*e.g.* for the treatment of rheumatoid and allied inflammatory conditions) is that often they are effective only at comparatively high dose-levels, at which unpleasant side-effects are rather common. A better understanding of the mechanism through which inflamed tissue can be "conditioned" or sensitized to antiphlogistic corticoids might show us how to obtain optimal effects with relatively low and safe doses (Selye, 1952; Selye and Horava, 1953).

The purpose of this communication is to report upon experiments in which the common bile-duct was severed in adrenalectomized rats which were maintained either with an antiphlogistic (cortisone) or a prophlogistic (desoxycorticosterone) hormone. A standardized, objectively-measurable inflammatory focus was then produced as an indicator of

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the animals' phlogistic potential. Here, the obstruction of the bile-duct could not have altered the secretion of corticoids, since the animals had no adrenals, but it could still influence the efficacy of the corticoids administered to them at an unvaried daily dose-level.

Experimental Materials and Techniques

Experimental Animals and their Maintenance.—Six groups of animals, each consisting of ten female Sprague-Dawley rats, were used. Their treatment as well as their initial and final body weights are listed, together with our findings, in the Table. All animals were fed on "Purina Fox Chow" and, since fifty of them were adrenalectomized and in need of sodium supplements, for uniformity's sake, all received 1 per cent. NaCl as drinking fluid.

"Granuloma-Pouch" Technique.—For the production and quantitative assessment of a long-lasting inflammation, the "granuloma-pouch" technique was used. The details of this procedure have been described elsewhere (Selye, 1953a, 1953b), but it should be stated here that the principle of the procedure is to inject 25 ml. air under the shaved dorsal skin of the rat, this being immediately followed by the introduction of some irritant into the regularly shaped, ellipsoid connective-tissue chamber thus formed. In the present experimental series, 0·5 ml. of 0·5 per cent. croton-oil solution (in corn oil) was used as a topical stressor to stimulate inflammation. The resulting amount of haemorrhagic inflammatory exudate can be assessed approximately, day-by-day, by transillumination of the pouch with an electric flashlight; it can subsequently be measured accurately by withdrawing the fluid into a graduated syringe. This measurement served as an objective indicator of inflammation and was performed after the animals were killed, on the 12th day following the preparation of the pouch. The granulomatous wall itself was not weighed in this experimental series, but macroscopical inspection and the assessment of its width on histological sections showed that there is a close parallelism between the volume of the exudate and the thickness of the granulomatous pouch.

Topical Irritation Arthritis.—On the 12th day, 2 hrs before the animals were killed, a so-called topical irritation arthritis test was performed in all groups. This enabled us to compare the behaviour of the more chronic exudative type of inflammation in the pouch, with that of an acute "anaphylactoid" reaction. The latter can be obtained by injecting certain agents to which the rat is hypersensitive (*e.g.*, egg-white, dextran, globin, etc.) into the subcutaneous tissue of the paw. The significance of this "anaphylactoid inflammation" has been described in several earlier publications (Selye, 1937b; Jasmin and Robert, 1953) and need not be discussed here. In the present experiment, 0·2 ml. of 0·2 per cent. dextran solution (prepared by diluting the commercial 6 per cent. dextran 1 : 30 with water) was injected under the plantar skin of the left hind-paw of each rat. The anaphylactoid inflammatory oedema was then objectively assessed by comparing the weights of both hind paws after amputation through the ankle joint. If the paw is amputated without previous fixation, much of the inflammatory fluid is lost. Hence, immediately after death, the hind limb was resected at the knee-joint and fixed in Bouin's solution; 24 hrs later the oedematous inflamed tissue became hardened and the paw could be cut off, with a sharp incision through the tibio-tarsal joint, without loss of fluid.

Adrenalectomy.—All adrenalectomies were performed under ether anaesthesia through the lumbar approach, 48 hrs before the preparation of the granuloma-pouch. This interval permitted the elimination of circulating corticoids and recovery from the operation.

Corticoid Substitution Therapy.—In Groups II and III, 1 mg. cortisone acetate microcrystals in 0·2 ml. suspending agent was given subcutaneously daily; in Groups V and VI, desoxycorticosterone acetate (DCA) microcrystals were administered at the same dose-level and in the same manner.

Bile-Duct Ligature.—The ligature of the common bile-duct was performed in Groups IV, V, and VI, under ether anaesthesia, immediately after the granuloma-pouch was prepared. A mid-line incision was made in the epigastric region through the shaved abdominal wall, and the duodenum was exteriorized. This exposed the bile-duct which was freed from adjacent pancreatic tissue just above its entrance into the gut, and transcised between two ligatures. After this, the abdominal wall was closed with three stitches.

Results

On the 12th day after the preparation of the granuloma-pouch, all animals were killed with chloroform, the exudate was measured as outlined above, and the thymus, spleen, preputial glands, both hind-paws, and a specimen of the granuloma-pouch wall, were fixed in Bouin's solution for histological study. All these organs—except the segment of granuloma-pouch—were also weighed (Table, overleaf).

Body-Weight.—It will be noted that there was no significant loss in any of the groups, but the normal growth was suppressed by the bile-duct ligature in the intact (Group IV) and the adrenalectomized-cortisone-treated (Group V) rats. The final body-weight of both DCA-treated groups was comparatively high and almost the same, whether they suffered from jaundice (Group VI) or not (Group III). This may have been due partly to imperceptible oedema-formation, under the influence of the sodium-retaining corticoid. However, among the jaundiced animals, the absence of body-weight loss was undoubtedly also conditioned by the fact that catabolism during jaundice (as in many other conditions of stress) is largely dependent upon the availability of gluco-corticoids.

TABLE

EFFECT OF BILE-DUCT LIGATURE UPON VARIOUS ACTIONS OF CORTICOIDS

Group	Treatment	Body-Weight (g.)		Exudate (ml.)	Thymus (mg.)	Spleen (mg.)	Preputial Glands (mg.)	Hind Paw (mg.)		
		Initial	Final					Right	Left	Difference
I	None	138±6·5	152±9	9·2±0·77	225±10·3	506±29	123± 6·4	1,309±15·5	1,852±51	543
II	Adrenalectomy + Cortisone	138±7·2	149±3·9	5·1±3·7	179±16·6	489±38	117±10·5	1,336±20·9	2,029±44·3	693
III	Adrenalectomy + DCA	138±2	167±3	11·3±1·3	367±21·6	715±39	117± 9·1	1,455±26	2,238±44	783
IV	Bile-duct Ligature	139±2	141±3·3	0·6±0·5	166±12·7	471±50·6	83± 8·9	1,288±17	1,920±50·5	632
V*	Adrenalectomy + Cortisone + Bile-duct Ligature	138±2·44	134±2·16	0	55± 7·9	386±50·1	89± 7·1	1,341±74	1,683±91	342
VI	Adrenalectomy + DCA + Bile-duct Ligature	142±1·56	161±9·8	6·8±1·35	272±22·5	787±80·5	94±12·4	1,443±25	2,077±46	634

* In three animals of Group V, the pressure of the accumulating bile caused a rupture of the distended bile-duct, with secondary peritonitis. These animals have not been included in the Table.

Inflammatory Exudate.—The formation of exudate was markedly, but incompletely, suppressed by bile-duct ligature in the intact rats (Group IV). On the other hand, not a single adrenalectomized rat maintained on cortisone showed the slightest trace of exudate formation after ligature of the bile-duct (Group V). As a matter of fact, even the connective tissue lining the granuloma-pouch showed no evidence of any response to the direct effect of croton oil. Conversely, in the DCA-treated-adrenalectomized rats (Group VI), the ligature of the bile-duct failed to suppress inflammatory exudate formation. The apparent difference between the volume of exudate in this group and in the adrenalectomized-DCA-treated controls, in which the bile-duct was not ligated (Group III), was statistically not significant (the value of "*P*" being between 0·4 and 0·5). In other words, under our experimental conditions, jaundice diminished inflammatory exudate formation in the presence of the adrenals; after adrenalectomy this effect was accentuated in animals maintained on cortisone and counteracted in those maintained on DCA. Thus there was a true synergism between the effects of cortisone and of jaundice in the adrenalectomized rat. This view is substantiated by the observation that the same dose of cortisone, given to adrenalectomized animals with intact bile-ducts (Group II), caused only a moderate depression of exudation, as compared to the untreated controls (Group I). These findings are perhaps even more striking when we contemplate dissected preparations of the granuloma-pouches, as represented in Fig. 1 (opposite).

Thymus.—Involution is an excellent indicator of the lympholytic effect of antiphlogistic corticoids, and this action roughly parallels their anti-inflammatory potency. It is noteworthy, therefore, that, in adrenalectomized controls (Group II), the dose of cortisone used in these experiments resulted only in a slight depression of the thymus-weight below that of the intact untreated controls (Group I). The thymus of the adrenalectomized-DCA-treated rats (Group III) was actually larger than that of the intact controls. This confirms that DCA, a prophlogistic corticoid, has no thymolytic effect. It should not be considered as a proof of an actual thymotrophic action, however, since adrenalectomy in itself notoriously results in some thymus enlargement, due to the elimination of all endogenous antiphlogistic (cortisone-like) hormones. It is also noteworthy that in intact rats (Group IV), the thymolytic effect of jaundice was much less pronounced than in adrenalectomized-cortisone-treated animals (Group V). In the latter, virtually the entire parenchyma of the organ had disappeared and only the stromal structures—which usually weigh about 40-60 mg.—were left. Thus, here again, there is a true synergism between jaundice and cortisone. This could not have been due merely to an increased secretion of cortisone-like compounds under the influence of jaundice, since these rats were adrenalectomized. No such synergism was noted between jaundice and DCA in adrenalectomized animals (Group VI), and it is even doubtful whether, under these conditions, the ligature of the bile-duct had any effect upon thymus weight. It is true that here, the mean weight of the organ is slightly below that of adrenalectomized-DCA-treated controls (Group III),

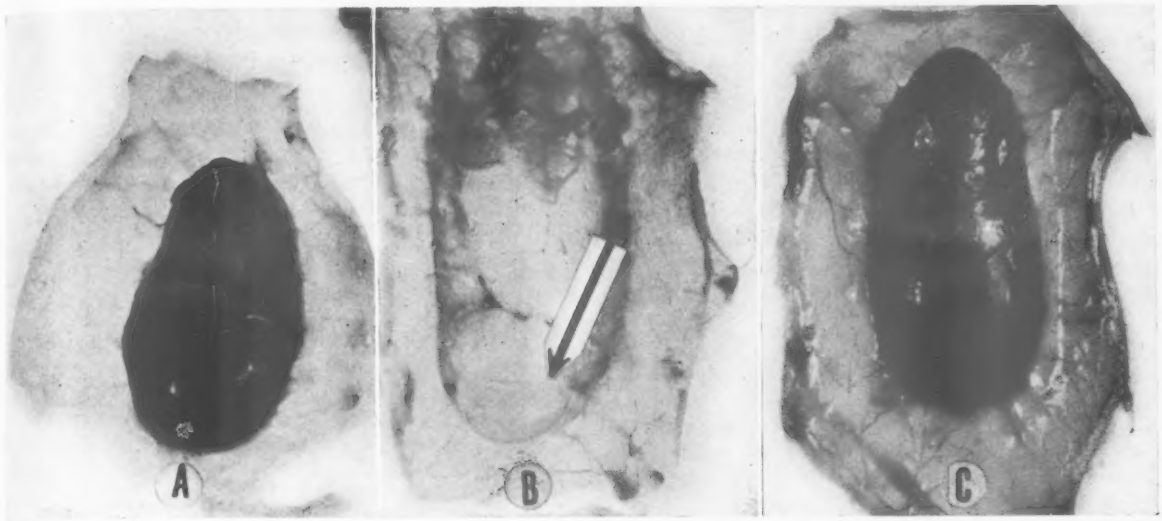

Fig. 1.—Macroscopic aspect of three granuloma-pouches.

The specimens represent the dorsal skin with the granuloma-pouch still adherent (viewed from attached side), as it appears at autopsy.

A. Group II: adrenalectomy + cortisone. Control without bile-duct ligature. Note well-developed ellipsoid granuloma-pouch, approximately half-filled with dark haemorrhagic inflammatory exudate.

B. Group V: adrenalectomy + cortisone + bile-duct ligature.

Suppression of exudation is complete. The concave, upper level of the colourless croton-oil solution is just visible at the level indicated by the arrow. There has been no formation of haemorrhagic exudate and even the tissues in direct contact with the irritant exhibit no evidence of an inflammatory reaction. Note also that the air-chamber is flat, because of absence of the usual contraction which takes place in inflamed connective-tissue and gives the well-developed granuloma-pouch its definite shape and hard consistency. The connective tissue which forms the wall is completely transparent. The irregular, greyish masses near the upper pole are particles of interscapular fat, which could not be dissected from the thin connective tissue membrane of the pouch.

C. Group VI: adrenalectomy + desoxycorticosterone + bile-duct ligature.

Unlike in the rats maintained on cortisone here, inflammation is not suppressed, despite the intense jaundice.

but statistically, the difference is not significant (the value of "*P*" being between 0·1 and 0·2).

Spleen.—This is only partly lymphoid, and usually tends to respond less markedly but in the same manner as the thymus in animals treated with cortisone or exposed to stress. This is essentially confirmed by the present experimental series. We noted only an insignificant decrease of splenic weight in intact jaundiced animals (Group IV); this involution was greater (though not significantly so) in the adrenalectomized-cortisone-treated rats (Group V), and was completely absent in adrenalectomized-DCA-treated rats (Group VI). In fact, in the latter group, the weight of the spleen was the same (the apparent increase is not statistically significant) as in the adrenalectomized-DCA-treated controls without bile-duct ligature (Group III).

Preputial Glands.—Considerable importance is attached to the response of these glands, for reasons which will be explained in the discussion. Meanwhile, let us merely point out that, irrespective of all other variables, in the three groups of jaundiced animals, the weights of these glands were actually somewhat below normal. In comparing any one jaundiced group with the corresponding non-jaundiced group, this atrophy is of doubtful statistical significance. However, its constancy in all three groups with bile-duct ligature is highly suggestive and, in any event, for our interpretation, the important fact is the absence of a preputial-gland hypertrophy.

Topical Irritation Arthritis Test.—This was evaluated on the basis of the difference between the right (control) and left (dextran-injected) hind paws. Under the circumstances of this experiment, DCA produced no significant change in any of the groups, while cortisone induced a noteworthy inhibition of inflammatory swelling only in the adrenalectomized-jaundiced rats (Group V). That this particularly acute type of inflammation is more difficult to influence with hormones than the more chronic process in the granuloma-pouch, agrees with the observations of most workers in this field, including our own. It is noteworthy, however, that even here, a definite sensitization to cortisone could be induced in adrenalectomized animals by the ligature of the bile-duct.

Discussion

From these experiments, it is evident that in intact rats, ligature of the common bile-duct affects inflammation and the lymphatic organs in the same manner as a heavy overdosage with antiphlogistic corticoids. In particular, it inhibits inflammatory exudate-formation and causes involution of the thymus.

In analysing the mechanism through which these effects might take place, the following questions arise:

(1) *Are the antiphlogistic and thymolytic effects of bile-duct ligature merely due to the non-specific stress of this surgical intervention, or to the resulting retention of bile?*

In order to examine this point, a subsidiary experiment was performed on ten intact rats, comparable in every respect to those of Group IV, except that the bile-duct was not ligated but merely exposed and freed of surrounding pancreatic tissue. Here, the mean volume of exudate accumulated during 12 days in the granuloma-pouch ($8 \cdot 9 \pm 0 \cdot 89$) and the weight of the thymus ($218 \pm 9 \cdot 5$) were essentially the same as in the intact controls (Group I) of the present experimental series. It may therefore be concluded that the stress of the surgical operation itself was not the decisive factor. It still remains to be seen whether the jaundice acted specifically through some components of the retained bile, or through damage to the liver, caused by the mere pressure of its accumulating secretion.

(2) *Is the synergism between bile-duct ligature and cortisone a mere summation or an actual potentiation of their individual actions?*

We doubt whether this question can be definitely answered on the basis of our experiments, but consider the latter possibility to be more probable. It will be recalled that the effect of bile-duct ligature upon exudation and thymolysis was not statistically significant in DCA-treated-adrenalectomized animals; yet, in cortisone-treated-adrenalectomized rats, the experimental jaundice caused complete inhibition of exudation and virtually total involution of the thymus. A mere summation of effects is rendered even less likely when we consider the topical irritation arthritis as an indicator of inflammation and the changes in the splenic weight as a sign of lympholysis. In adrenalectomized animals, a definite inhibition of the arthritis with splenic atrophy was observed only in jaundiced rats treated with cortisone. As judged by the lack of response of adrenalectomized-DCA-treated rats, jaundice exerts no direct effect either upon the arthritis or upon splenic weight. In any event, however,— be this summation or potentiation—it is clear that even after adrenalectomy jaundice "conditions" inflamed and lymphatic tissue to the inhibitory effect of cortisone and hence that it must act through some extra-adrenal mechanism.

(3) *Could this conditioning effect of jaundice be mediated through the discharge of endogenous ACTH?*

The channels through which various systemic stressor agents condition the body to the actions of antiphlogistic corticoids, such as cortisone, have been reviewed at some length in another publication (Selye, 1954). These possible pathways are schematically outlined in Fig. 2.

The topical response (*e.g.* inflammation, cell-degeneration, and necrosis) to a local stressor, in our case croton oil, can be influenced by a systemic stressor, in our case jaundice, through a dual mechanism:

(I) The systemic stressor induces an ACTH-discharge by the pituitary; this leads to an increased secretion of antiphlogistic corticoids (A-C) of the cortisone-type. The latter inhibit inflammatory phenomena by virtue of their direct effect upon mesenchymal tissues (represented here by a fibroblast).

(II) This effect is greatly enhanced by some non-adrenal-mediated "antiphlogistic-corticoid-conditioning-factor(s)" (A-CC). It has not yet been established whether this A-CC is related to the "first mediator" (designated here by a question mark), which is responsible for the ACTH-discharge during stress. There is some evidence, however, that ACTH itself may—in addition to its trans-adrenal action—possess such a peripheral A-CC effect (dotted line).

Experimental evidence, suggesting the existence of such a non-adrenal-mediated direct action of ACTH, has been presented in several previous publications (Jacot and Selye, 1952; Selye, 1951; Selye and Jacot, 1952). In particular, it had been shown that various impure ACTH preparations cause involution of the thymus in adrenalectomized rats maintained

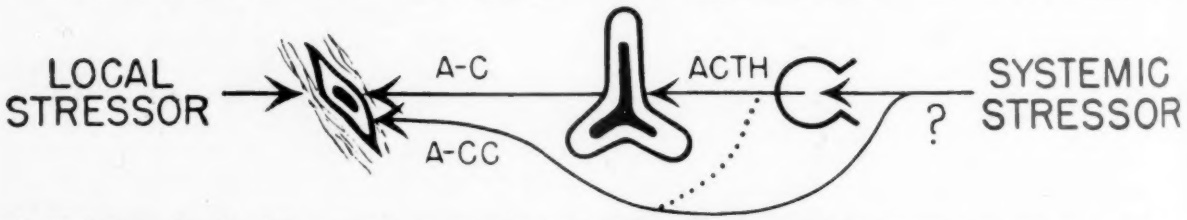

Fig. 2.—Pathways through which a systemic stressor agent (*e.g.*, jaundice) could affect inflammatory responses to local stress (*e.g.*, that caused by a chemical irritant such as croton oil)

on very small doses of cortisone, which, in themselves, are inactive in this respect. However, this thymolytic effect was not obtained with more purified ACTH preparations; hence, the possibility had to be considered that the thymolytic factor-present in impure preparations, is either a separate hormone, or merely the manifestation of systemic stress caused by impurities. The latter possibility is rendered rather probable by other observations of this laboratory (Selye, 1950; Herlant, 1950). It was noted that in adrenalectomized rats—maintained exclusively with salt supplements to their diet—there is no thymolysis during systemic stress, but that marked thymolysis occurs if they are maintained with small doses of cortisone, which in themselves are ineffective.

Another extra-adrenal action of ACTH-containing extracts is their ability to stimulate the preputial glands of the rat. Unlike the thymolytic action, the effect upon the preputial glands was obtained even with the most purified preparations of ACTH (Jacot and Selye, 1952; Selye and Jacot, 1952). In recent (hitherto unpublished) experiments we confirmed this also with the highly purified "Corticotropin-B".* It cannot be excluded that even the best available ACTH preparations are contaminated with a separate trophic hormone for the preputial glands, but we have no factual evidence for this assumption. It is of special interest, therefore, that jaundice caused no hypertrophy of the preputial glands in any of our rats. Unless the preputial-gland-stimulating effect of ACTH preparations is due to a contamination, it may be concluded, therefore, that the A-CC action of jaundice is not mediated by a direct effect of endogenous ACTH (as indicated by the dotted line in our drawing). This is all the more noteworthy, since Hess and others (1952) claimed that the systemic stress caused by burns is associated with a stimulation of the preputial glands which they ascribed to the discharge of endogenous ACTH. It is undoubtedly true, furthermore, that jaundice does cause an adreno-cortical enlargement, which is presumably mediated through the discharge of ACTH; hence this aspect of our findings cannot be adequately explained at present. There is some reason to suspect the existence of several kinds of ACTH. It is possible that the corticotrophic principle secreted during jaundice is insufficient in amount or that it is devoid of any preputial-gland-stimulating action. Furthermore, this particular effect of the hormone may be suppressed by some other action of jaundice. Be this as it may, the observations described in this communication offer no support for the assumption that the A-CC effect of jaundice is mediated through some extra-adrenal action of ACTH.

In conclusion, it may be said that our experiments furnish definite evidence in favour of the view that the well-known anti-inflammatory effect of jaundice is not merely due to a direct action upon connective tissue, nor exclusively mediated through the stimulation of antiphlogistic-hormone secretion. It depends, at least to a considerable extent, upon a peripheral synergism between antiphlogistic corticoids and some extra-adrenal "conditioning" effect of the jaundice. Although our diagram deals only with inflammatory changes, the same factors appear to be involved in the lympholysis caused by jaundice, except that here no topical stressor is applied to the target-organ directly.

* Kindly supplied by Merck and Co., Inc.

Summary

Jaundice, experimentally induced by ligature of the common bile-duct, inhibits inflammation in the rat. This can be assessed in quantitative terms by the measurement of exudation in the "granuloma-pouch" test. At the same time, jaundice also causes pronounced involution of the thymus.

These effects of jaundice are not merely the result of an increased antiphlogistic-corticoid production, since they are evident even in adrenalectomized animals, maintained on small doses of cortisone (in themselves virtually ineffective).

In adrenalectomized rats, maintained with desoxycorticosterone (which is devoid of antiphlogistic actions), this effect of jaundice is either absent, or very slight.

Jaundice (like most other agents which cause intense systemic stress) increases the secretion of ACTH, and consequently of antiphlogistic corticoids; yet it is not primarily through this mechanism, nor through a direct peripheral effect of the bile, that it inhibits inflammation or causes thymolysis.

The experiments suggest that the intense inhibition of inflammatory and lymphatic tissues by jaundice is primarily due to a conditioning or sensitization of the tissues to antiphlogistic corticoids, the so-called "A-CC effect".

The author is greatly indebted to Doctor Ernesto Salgado for all statistical calculations, and to Mr. Kai Nielsen, Miss M. Langlois, and Miss R. Prud'homme for technical assistance, including the preparation of the illustrations.

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Sur le mécanisme par lequel l'ictère par rétention influence le processus inflammatoire

RÉSUMÉ

Un ictère reproduit expérimentalement par la ligature du canal biliaire inhibe l'inflammation chez le rat. Ceci peut être déterminé quantitativement par la mesure de l'exsudat dans la "poche granulomateuse". En même temps l'ictère produit l'involution du thymus.

Ces effets de l'ictère ne dérivent pas simplement de la production corticoïde antiphlogistique augmentée, puisqu'ils se voient aussi chez des animaux adrénalectomisés et maintenus par de petites doses de cortisone (étant seules virtuellement sans effet).

Chez des rats adrénalectomisés maintenus par la desoxycorticostérone (qui n'a pas d'action antiphlogistique) cet effet de l'ictère est léger ou absent.

L'ictère (comme tout agent qui produit un état d'intense fatigue générale) augmente la secrétion de l'ACTH et par conséquent des corticoïdes antiphlogistiques; toutefois, ce n'est pas en premier lieu par ce mécanisme ni par un effet périphérique direct de la bile qu'il inhibe l'inflammation ou produit la thymolyse.

Les expériences suggèrent que l'inhibition intense des tissus inflammatoires et lymphatiques par l'ictère est due en premier lieu au conditionnement et à la sensibilisation des tissus aux corticoïdes antiphlogistiques, autrement dit à "l'effet A-CC".

Sobre el mecanismo por el cual la ictericia obstructiva afecta el proceso inflamatorio

SUMARIO

Una ictericia inducida experimentalmente por la ligatura del conducto biliar común inhibe la inflamación en la rata. Esto se puede determinar cantitativamente al medir el exudato en la "bolsa granulomatosa". Al mismo tiempo la ictericia produce la involución del timo.

Estos efectos de la ictericia no resultan meramente de la producción corticoide antiflogística aumentada, ya que se observan también en animales adrenalectomizados y mantenidos con pequeñas dosis de cortisona (por si virtualmente sin efecto).

En ratas adrenalectomizadas mantenidas con desoxicorticosterona (que no tiene acción antiflogística) este efecto de la ictericia es débil o ausente.

La ictericia (como todo agente que produce intensa fatiga general) aumenta la secreción de la ACTH y por consiguiente de los corticoides antiflogísticos; sin embargo, no es en primer lugar este mecanismo ni el efecto periférico directo de la bilis que inhibe la inflamación y produce la timolisis.

Los experimentos sugieren que la inhibición intensa de los tejidos inflamatorios y linfáticos por la ictericia se debe en primer lugar al acondicionamiento y a la sensibilización de los tejidos a los corticoides antiflogísticos, llamado "efecto A-CC".

ANKYLOSING SPONDYLITIS AND PROLONGED ACTH THERAPY

BY

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(RECEIVED FOR PUBLICATION APRIL 5, 1954)

The maintenance of prolonged adrenal stimulation by the administration of ACTH is still an experimental procedure and as yet little detailed information on the subject has been published. The six cases described below are presented as much for the light they throw on this subject as for the information they provide about the benefits that patients suffering from ankylosing spondylitis may derive from this form of therapy. The six patients received ACTH continuously for from 1½ to 2 years. During the latter half of the treatment period adrenocortical activity was studied by assays of urinary 17-ketosteroids (17-KS) and urinary 17-ketogenic steroids (17-KGS), using the methods described by Norymberski and others (1953).

The majority of patients with ankylosing spondylitis can be treated satisfactorily with aspirin, phenylbutazone, and deep *x*-ray therapy. Their spines can be kept straight, they can be kept at work most of the time, and in many the movements of the thorax can be maintained. Severe cases, unfortunately, derive only temporary relief from deep *x*-ray therapy, and when their hip joints are affected they suffer considerable permanent disability. It was patients considered to be of this type who were selected for prolonged ACTH therapy.

In addition to the observations recorded below, monthly estimations of haemoglobin, packed cell volume, white blood count, plasma proteins, fibrinogen, and cholesterol were made. These have not been recorded in the diagrams because it was thought that the minor variations observed were of insufficient interest.

Case Reports

Case 1, a man aged 30, was, in our opinion, beyond any but palliative treatment when first seen. The entire spine and thorax were rigid, the hip joints were largely destroyed, and all the peripheral joints were swollen and tender. The fingers were hyperextended and powerless and the feet and toes plantar flexed. The bones of all the joints were grossly osteoporosed and he had multiple small renal calculi. He had lain helpless for the preceding 9 months. In addition to the ACTH and cortisone acetate therapy he had much active physiotherapy and manipulation. Seven months after starting treatment he was walking unaided, had a strong grip, and was able to attend to all his own needs. The chart tells its own story. The record of symptoms represents a clinical impression of the degree of pain, stiffness, and disability attributable to the active disease process; 100 per cent. denotes a state of complete helplessness, with all its attendant pain, due to active disease, and 50 per cent. a state in which the patient can only get about with great difficulty, with the help of analgesics every 3-4 hours, again because of active disease. The main problem in this case was that of hypertension; the diastolic blood pressure rose to dangerous heights when he was away from hospital for 2 months on a dose of H.P. Acthar Gel that proved to be excessive (10 "units" twice daily). The rise in the urinary output of 17-KGS to above 100 mg., equivalent to a daily adrenal secretion of over 200 mg. hydrocortisone, suggests that the preparation used contained an adrenal growth factor (West, 1954). The fact that considerable adrenal stimulation continued when only 5 "units" were injected each day tends to confirm this. The most surprising happening in this case was that the bone density in the patient's hands returned almost to normal in less than 9 months (Figs 1*a* and *b*, 2*a* and *b*, overleaf). We have seen nothing like it in rheumatoid arthritis treated with ACTH or cortisone acetate. This suggests yet another point of difference between these two diseases. Of importance are the acute relapses with fever that occurred on the two days in February, 1954, when injections were missed (Fig. 3, overleaf). Sudden major reductions in dosage, after prolonged therapy, are dangerous in severe rheumatic diseases.

This patient is very grateful for the benefits that he has gained from treatment and we would advocate similar treatment for others like him but for the hypertension. Whether this treatment will prove valuable to him in the long run depends upon whether the hypertension can be overcome without the occurrence of a severe relapse. In the last few weeks he had been transferred to hydrocortisone 60 mg. daily by mouth. So far there has been no serious relapse and his blood pressure has begun to fall.

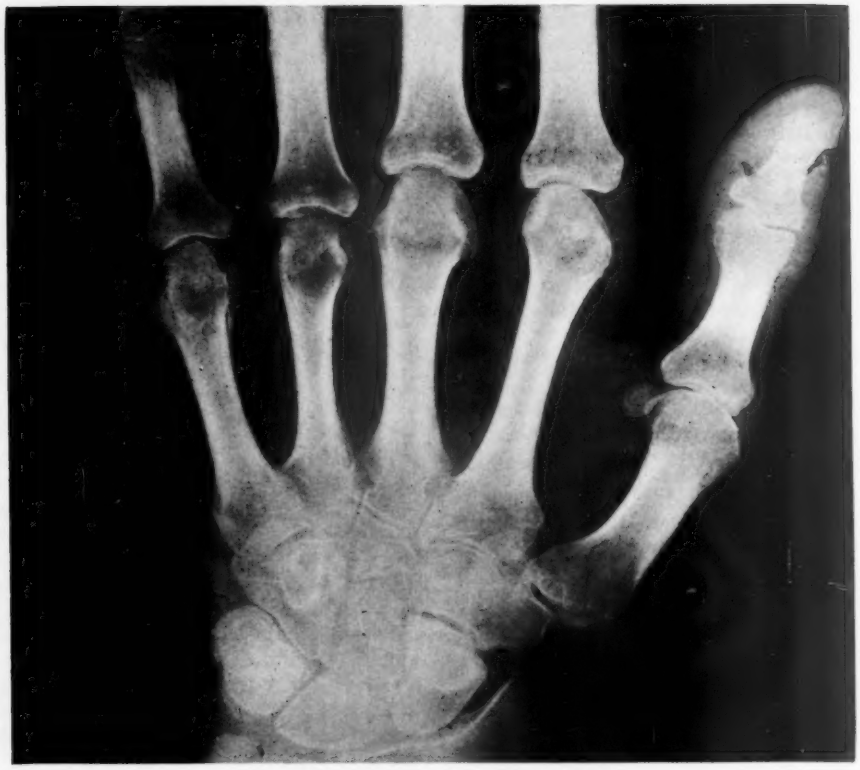

Fig. 1(*a*).—Case 1 in July, 1952, left hand.

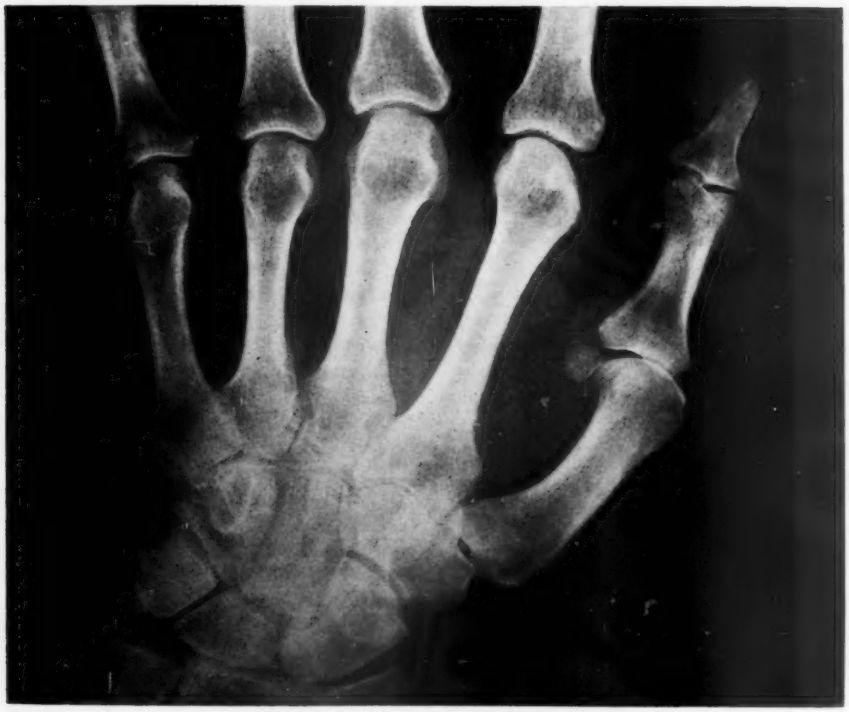

Fig. 2(*a*).—Case 1 in October, 1953, left hand.

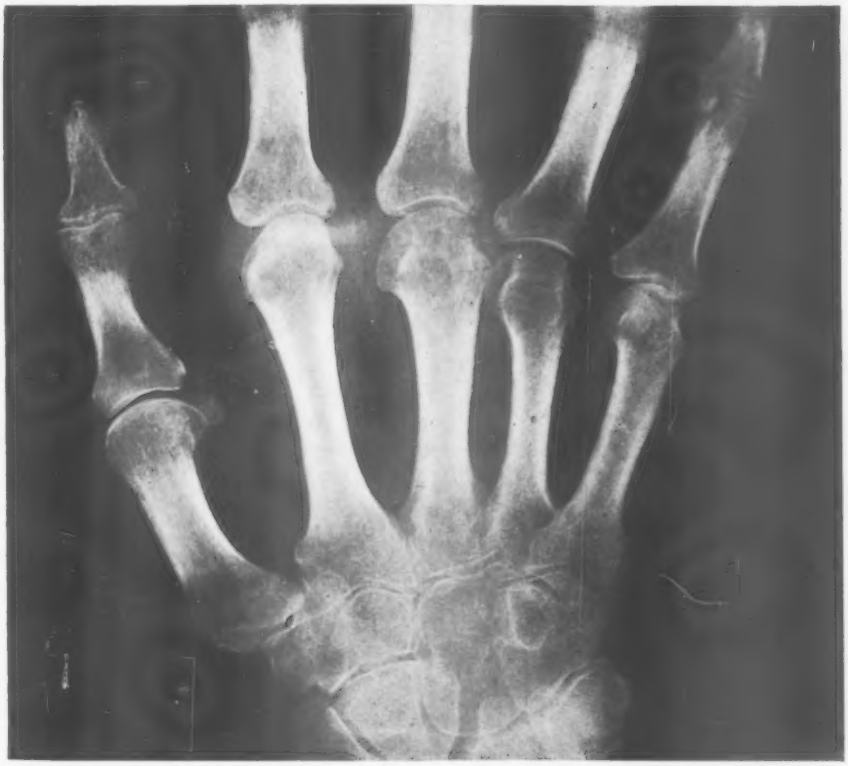

Fig. 1(*b*).—Case 1 in July, 1952, right hand.

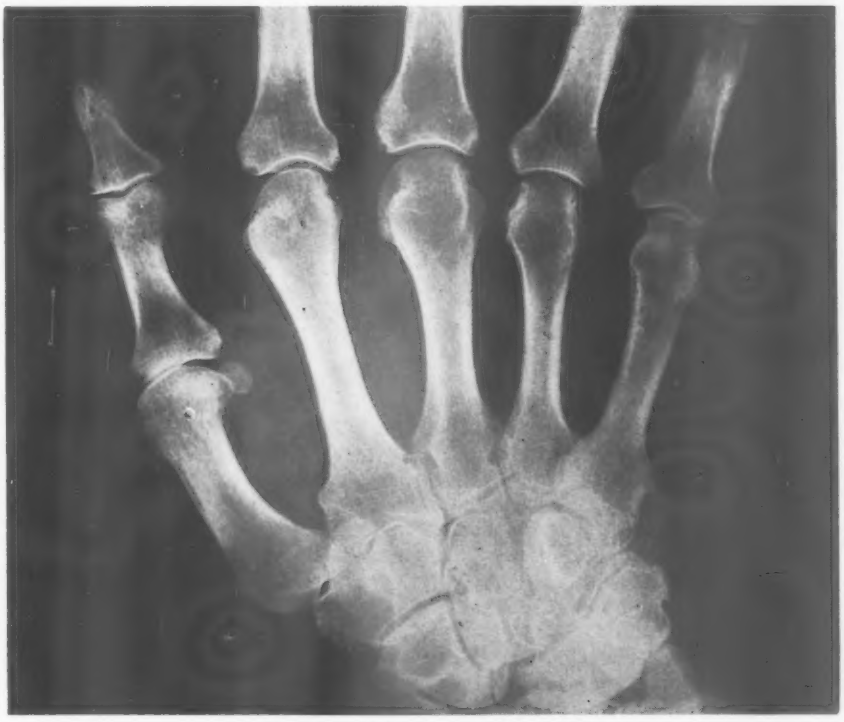

Fig. 2(*b*).—Case 1 in October, 1953, right hand

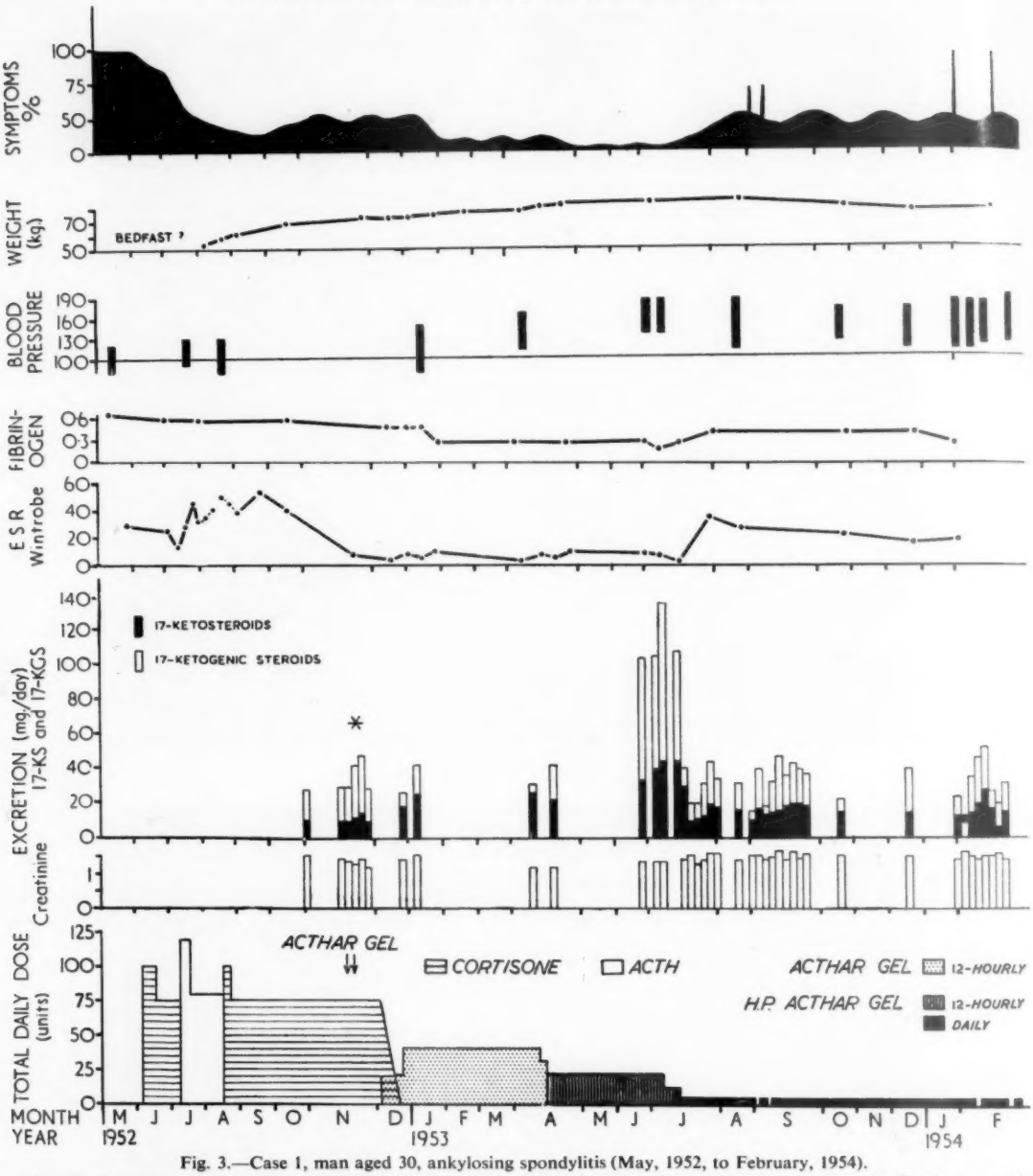

Fig. 3.—Case 1, man aged 30, ankylosing spondylitis (May, 1952, to February, 1954).

* A series of assays were made on November 25-29, 1952, and injections of Acthar Gel were given in addition to Cortisone on November 26 and 27, 1952.

Case 2, a man aged 36, was treated in the hope of saving his second hip joint, the first having already suffered considerable damage. His spine was rigid and, as in Case 1, he had already had as much deep *x*-ray therapy as it was safe to give. After a severe febrile relapse in February, 1952, he was rehabilitated, taught a new job at a technical college, and found a suitable post. The frequent changes in ACTH dosage reflect a running battle to keep the adrenal stimulation down in order to prevent hypertension. On a number of occasions he raised the dose himself so that he might not lose any time from work (!) Of particular note is the reversal of the 17-KS/17-KGS ratio during the latter months of his treatment. In this unit several hundred assays of the 17-KS and 17-KGS excretions have been made for patients receiving ACTH; it has been found that, at least in the early months of treatment, the excretion of 17-KGS always exceeds the excretion of 17-KS when the excretion of 17-KS has risen to above 25 mg. Exceptions sometimes occur on a day following a marked reduction in ACTH dosage. In this patient the excretion of 17-KGS fell in the course of a year by 100 per cent., yet the excretion of 17-KS remained unaltered. It is likely that the increased output of 17-KS seen during

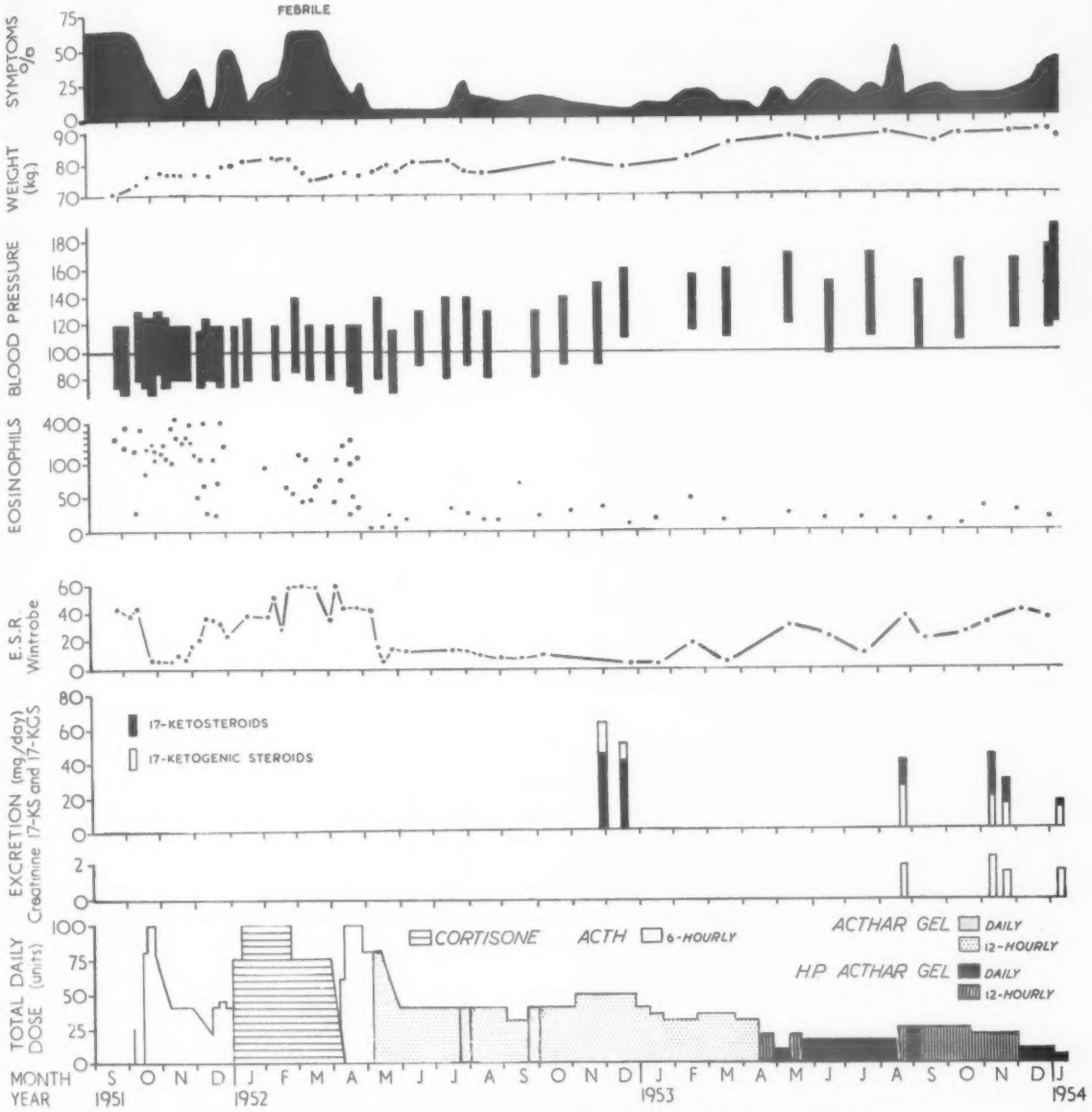

Fig. 4.—Case 2, man aged 36, ankylosing spondylitis (September, 1951, to January, 1954)

adrenal stimulation represents largely corticosteroid precursors and not degradation products as often supposed. The results of assays in August and November, 1953, suggest that either the adrenal had become less efficient in its synthesis of hydrocortisone or that the 17-KS increase represented, in part, precursors of some other corticosteroid. Now, in our experience of other patients receiving ACTH or cortisone acetate, an output of 20-25 mg. per day of 17-KGS, though long continued, is not accompanied by hypertension. Hence it is likely that some corticosteroid other than hydrocortisone was being secreted by this patient's adrenal. This other non-17-KGS corticosteroid might well have been corticosterone or even aldosterone (Simpson and others, 1954). The latter would, of course, be secreted in very small amounts and would not be expected to have a measurable effect upon the 17-KS excretion. If an adrenal steroid other than hydrocortisone were responsible for the sustained hypertension, one would expect the blood pressure to fall following the suppression of adrenocortical activity by withdrawal of ACTH therapy and the administration of hydrocortisone. Since the completion of Fig. 4 the ACTH injections have been stopped and 60 mg. hydrocortisone given daily. The blood pressure has fallen significantly (from 190/120 to 145/105) in the course of 8 weeks, although the output of 17-KGS

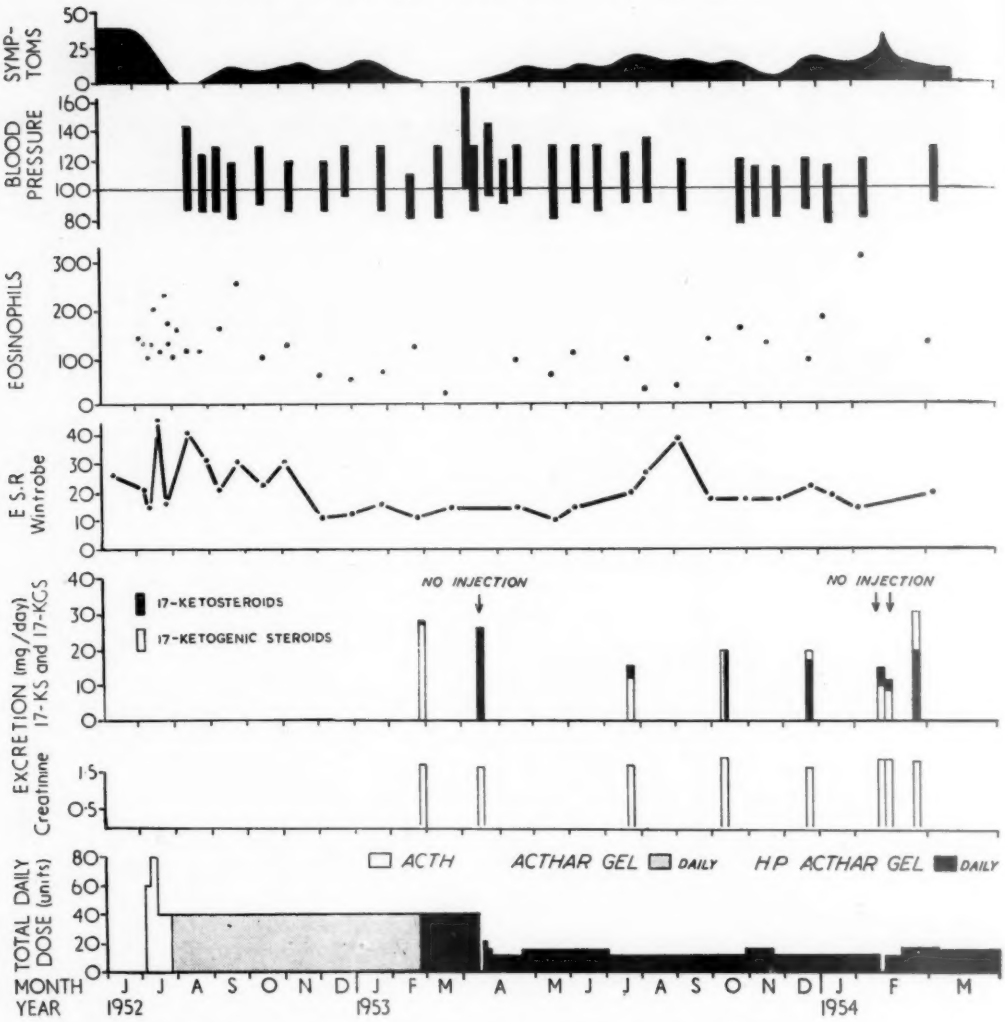

Fig. 5.—Case 3, woman aged 32, ankylosing spondylitis (June, 1952, to March, 1954)

has risen to 30 mg. (50 per cent. of administered hydrocortisone is normally recovered as 17-KGS). Whatever the interpretation of the altered 17-KS/17-KGS ratio in this case, this phenomenon must be considered as a complication of prolonged ACTH therapy.

This patient would say that he has derived benefit from this course of treatment, but we must conclude, since we cannot see into the future, that we may have done more harm than good. The right hip for which treatment was begun has remained symptom-free but both knees have become swollen and effused.

Case 3, a woman aged 32, was treated because of persistent groin pain in the hope that destructive changes in the hip joints might be prevented. She had had four courses of deep *x*-ray therapy. The lumbar and dorsal spine was rigid and the neck movements restricted by about 50 per cent. Fig. 5 shows what happens when Acthar Gel is replaced by H.P. Acthar Gel. When given in a single daily dose, as this patient had had throughout, these preparations are supposed to be equally potent. The H.P. unit contains one-third as much ACTH (assayed by the Sayers technique, Sayers and others, 1948) as the ordinary gel. When seen soon after changing to H.P. Gel the patient was "full of the wild joys", but by the end of the 6th week she felt blown up, extremely irritable, and tense, and could not sleep. To continue the dose in order to collect a 24-hr specimen for assay was not justified, but, from the result of the assay made on the 24-hr specimen when no injection had been given, one can deduce that on the previous day the output must have been very high.

The patient maintains that for the 20 months she has remained very much better and able to do more than before treatment. Clinically and radiologically the disease does not appear to have advanced.

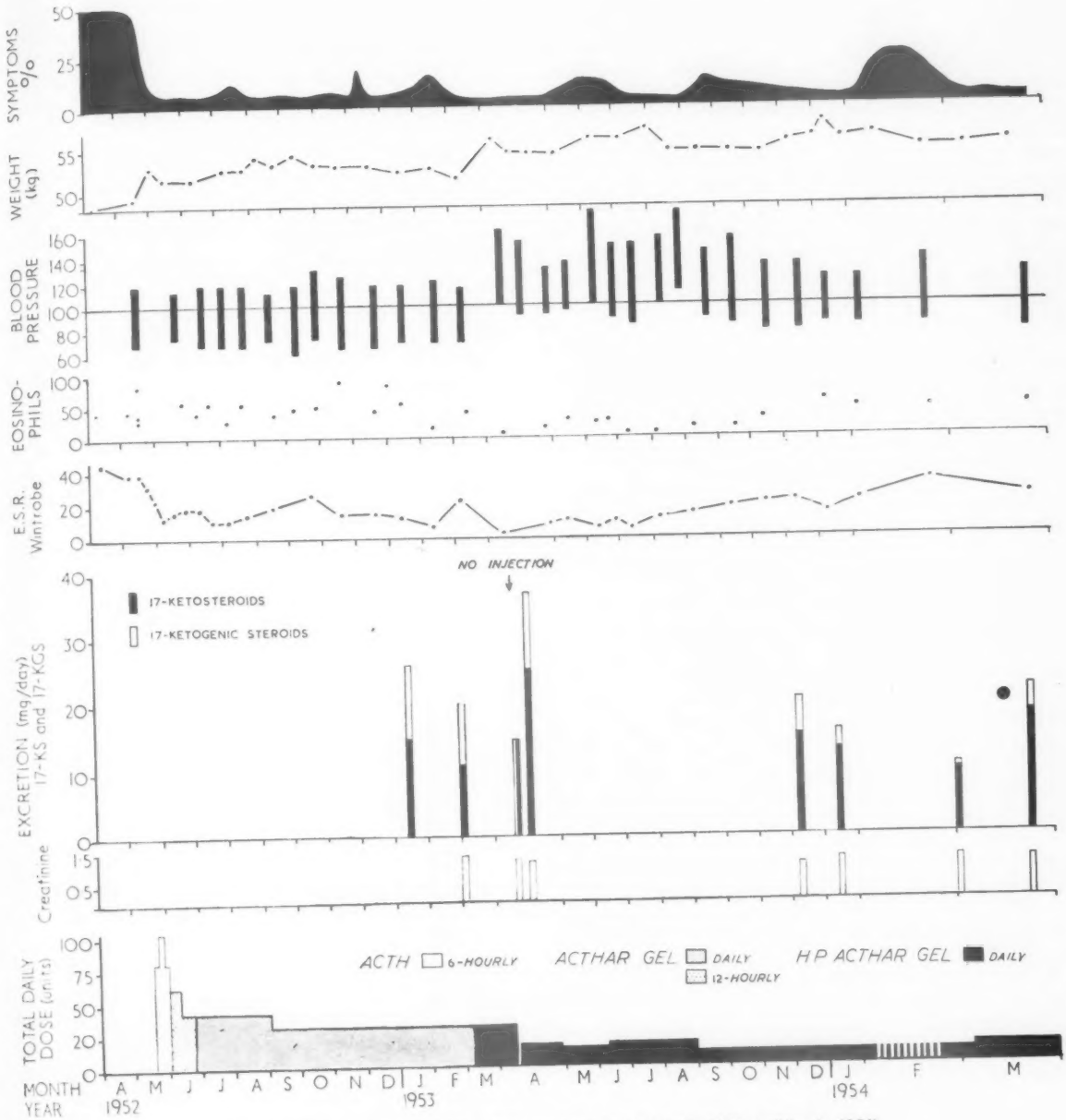

Fig. 6.—Case 4, woman aged 32, ankylosing spondylitis (April, 1952, to March, 1954)

Case 4, a woman aged 32. This patient's disease had run a comparatively mild course for 10 years. The lumbar and dorsal spine was rigid and the chest expansion ½". She came under treatment because of persistent groin pain, and within a few weeks of beginning treatment with ACTH she was able to resume full household duties. There has been no evidence of advance in the disease and her clinical state to-day remains better than before treatment. Minor relapses do not appear to be necessarily followed by further irreparable damage. Fig. 6 shows how a small change in the dosage, when long continued, can markedly affect the blood pressure. This patient had an episode similar to that experienced by Case 3 soon after starting H.P. Acthar Gel.

Case 5, a man aged 27.—The disease was less advanced in this patient; it had begun 2 years previously and two courses of deep *x*-ray therapy had revealed that the back stiffness and thoracic involvement were largely reversible. ACTH therapy was begun because the back and chest symptoms quickly returned after the second course of *x*-ray therapy, and because of early involvement of the left hip joint. The patient was then unable to work but he soon started again after treatment began and since then has only lost one week from work through his spondylitis. The eosinophil counts show how unreliable such figures may be in the assessment of adrenal stimulation; it is not our practice to make any deductions from them. In the latter months of treatment the adrenal stimulation was little above normal levels.*

That the ACTH was still producing some effect in this patient is made clear by the series of minor relapses that occurred on each day that treatment was missed in January, 1954. It could not be foreseen whether the endogenous supply of ACTH would start up slowly or quickly on cessation of treatment. Fig. 7 (opposite) shows that when the H.P. Acthar Gel was stopped adrenal stimulation was apparently resumed at once, "Butazolidin" (phenylbutazone)† being sufficient to control the symptoms. It must not be assumed from this experience that the endogenous supply of ACTH will return immediately in all cases after prolonged ACTH therapy. Further, the fact that normal amounts of 17-KGS were excreted after treatment was stopped does not necessarily mean that the pituitary will be able to respond adequately to the stress of major trauma.

Although in this case the disease has shown no evidence of advance during the last 1½ years, and although the patient's state to-day remains better than before treatment began, one cannot say that it would have been otherwise had he been treated upon more conservative lines. The patient himself claims great benefit and regards the seven hundred or more injections that he has given himself as a small price to have paid for it.

Case 6, a man aged 39, had suffered with pain on the back for 10 years. He was discharged from employment in the mines by a medical board with what was described as a "tuberculous spine". His spine and thorax were rigid and he began treatment because his knees continued to be tightly effused and very painful, in spite of repeated aspirations and the intra-articular injection of hydrocortisone acetate. In the autumn of 1953 the adrenal stimulation was little above normal levels and was clinically ineffective. Unless the adrenal output of hydrocortisone can be measured it is not possible to know whether a relapse is due to an increase in disease activity or to a decrease in the effective dose of ACTH.

To-day the patient's state is little different clinically or radiologically from what it was before treatment was begun. It remains to be seen whether a further increase in adrenal stimulation will control the symptoms without producing hypertension. The reversed 17-KS/17-KGS ratio of the last assay is not encouraging (Fig. 8, overleaf).

* Unfortunately there are no pre-treatment assays of 17-KGS for any of these cases as the assay was not in routine use when they began treatment. From the study of many patients since we have found that the pre-treatment level of excretion lies between 7 and 13 mg. 17-KGS per 24 hrs.

† Phenylbutazone in therapeutic doses does not cause adrenal stimulation.

Discussion

From the study of these six patients can one say that long continued adrenocortical stimulation has a place in the treatment of ankylosing spondylitis? The patients were selected as those most likely to run a difficult course, yet in five of the six the disease, as judged by physical signs and *x*-ray appearances, has not advanced, and only the first patient (Case 1) is not able to work. In spite of these findings the question can only be answered by a personal opinion, since these patients had no controls and the course of ankylosing spondylitis is so unpredictable. Our opinion is that in the really severe cases, who receive little benefit from deep *x*-ray therapy, prolonged adrenal stimulation is justified, but that it should not be raised to a higher level, nor maintained for a longer period, than is absolutely necessary. For the less severe cases it should be withheld pending the results of controlled therapeutic trials. This disease is sufficiently different from rheumatoid arthritis to justify a separate therapeutic trial as between adrenal stimulation, hydrocortisone, and deep *x*-ray therapy, plus in each case an agreed schedule of analgesics. Many authorities speak of ACTH therapy as "simply suppressive", but the profound changes seen in the first patient described lead us to question this statement.

Two complications, both due to adrenal stimulation, were encountered in this study: hypertension and altered adrenal function. A moderate "antirheumatic" effect can be maintained without hypertension, but when a greater effect is needed hypertension supervenes. A simple restriction of salt intake did not affect the hypertension. Rigid salt-free diets and the effect of hypotensive drugs were not studied. In Case 2 the hypertension did not appear to be due to an excessive secretion of hydrocortisone. The change in the pattern of 17-KS and 17-KGS excretion, seen in some patients after prolonged adrenal stimulation, is a new observation and must be studied further. Other complications have been ascribed to ACTH therapy. Some are clearly the direct result of this therapy or of its withdrawal, and many are common to long-continued cortisone acetate therapy.* Complications which may or may not be the direct result of this therapy include gastro-intestinal haemorrhage

* For an informative discussion see the Symposium published by the Mayo Clinic in November, 1953.

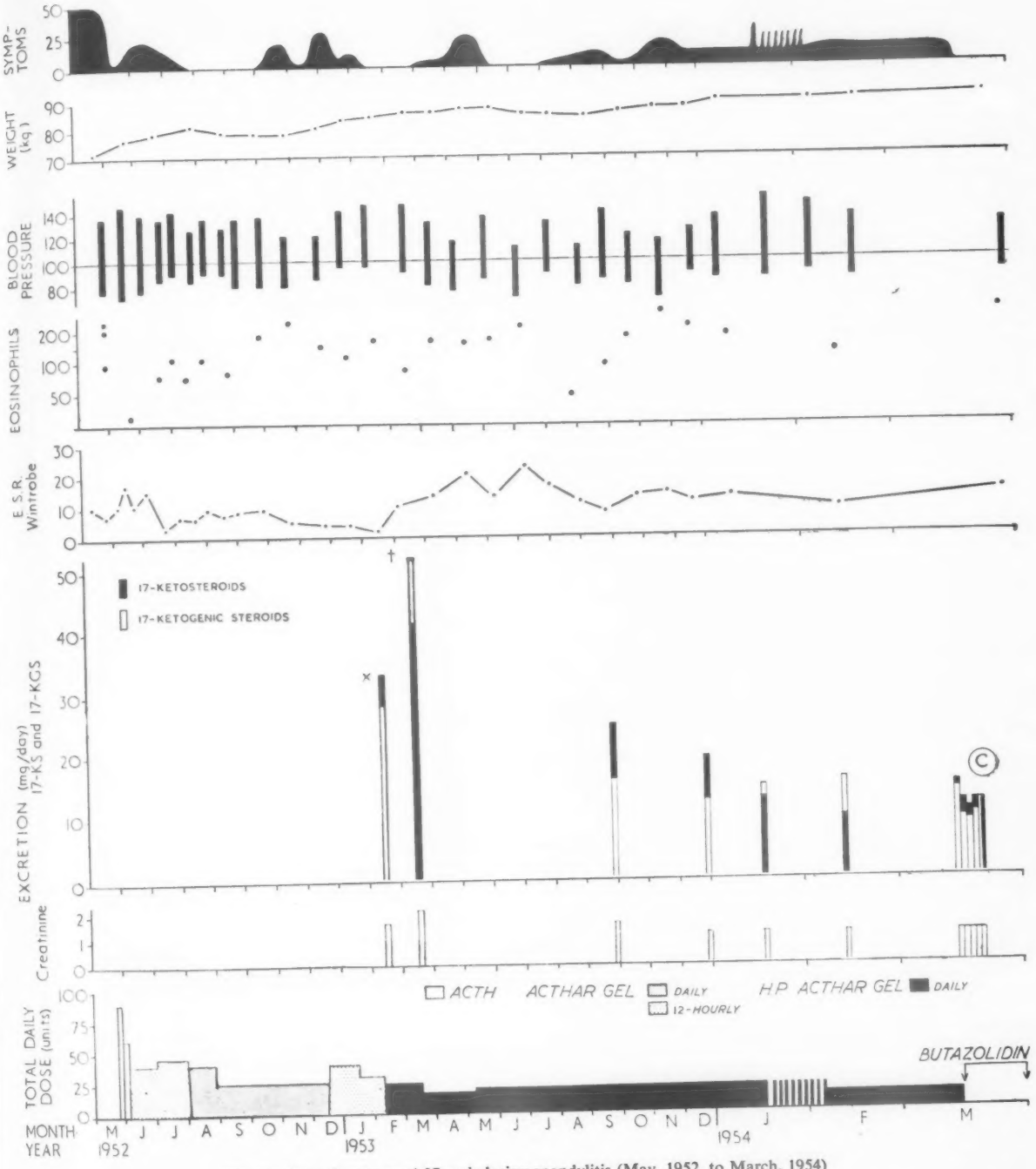

Fig. 7.—Case 5, man aged 27, ankylosing spondylitis (May, 1952, to March, 1954)

* On this occasion sugar was present in the urine. This may have considerably reduced the amount of 17-KGS assayed. Usually a modified technique is used to obviate this interference.

† On the day this 24-hr specimen was collected the patient had a high temperature. It was the first day of a brief illness described by his general practitioner as "influenza". The patient insists that the 24-hr collection was accurate.

ⓒ A correction was made for creatinine fluctuations in this group of assays. The average creatinine figure was taken.

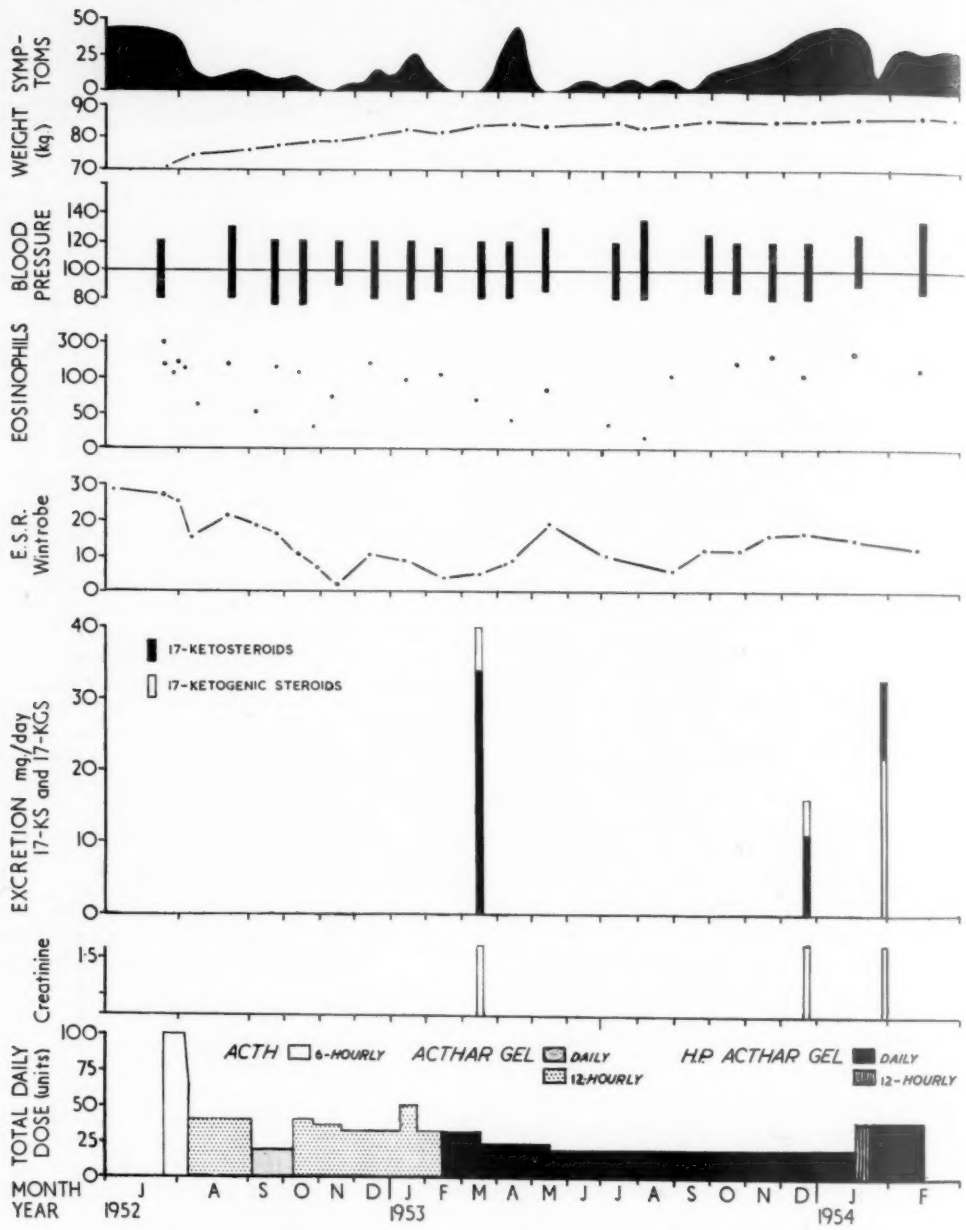

Fig. 8.—Case 6, man aged 39, ankylosing spondylitis (July, 1952, to February, 1954)

and intercurrent infection. Case 2 had an intestinal haemorrhage and Case 1 had two separate virus infections of note during the time of excessive adrenal stimulation: a Bell's palsy with vesicles in the ear, and herpes zoster affecting the 5th nerve, on opposite sides. The other oft-reported side-effects did not trouble these patients.

Figures 3-8 clearly show how impossible it is, even when using highly purified Acthar Gel, to lay down a dose schedule. Unless the 17-KS and 17-KGS excretions are estimated,* it is not possible to assess, except very crudely, the adrenal stimulus

* Other methods for assaying chemically, in urine, some of the corticosteroid metabolites of hydrocortisone and cortisone have been described, but they are time-consuming, unsuitable for the average hospital biochemical laboratory, and, it appears to us, less reliable. The same might be said of the assays of "17-hydroxy-steroids" in blood.

(*i.e.* the amount of treatment) that is being given. This being so, one wonders whether some of the conclusions drawn from therapeutic trials of ACTH given blindly may not need reconsideration. Our present practice is to assay a 24-hr specimen weekly until a maintenance level has been found, and then to make a monthly test.

Summary

(1) Six patients suffering from ankylosing spondylitis have been treated with ACTH for from 1½ to 2 years. Their progress is described.

(2) It is concluded that, as yet, prolonged adrenal stimulation is justified in only the most severe cases.

(3) Problems encountered in the control of ACTH therapy are illustrated and discussed.

(4) Evidence of adrenal dysfunction was seen in at least one patient; this condition is considered as a complication that may attend prolonged adrenal stimulation.

We wish to acknowledge the contributions made by other members of this unit, in particular the work of the sisters and of Mr. George Gibson and Mr. Bob Stubbs who performed the steroid assays. Part of the Acthar Gel used in this work was made available by the Medical Research Council and Nuffield Foundation Joint Committee on Cortisone and ACTH in Chronic Rheumatic Diseases, to whom our thanks are due.

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Traitement prolongé par l'ACTH de la spondylarthrite ankylosante

RÉSUMÉ

(1) Six malades atteints de spondylarthrite ankylosante furent traités pendant un an et demi à deux ans par l'ACTH. On décrit ici leur progrès.

(2) On conclut qu'à l'heure actuelle la stimulation surrénale prolongée n'est justifiée que dans des cas très graves.

(3) On éclaire et discute les problèmes rencontrés au cours du contrôle de la thérapie par l'ACTH.

(4) On a observé chez au moins un malade des signes de dysfonction surrénale; on considère qu'il s'agirait d'une complication de la stimulation surrénale prolongée.

Tratamiento prolongado con ACTH de la espondilitis anquilosante

SUMARIO

(1) Seis enfermos con espondilitis anquilosante fueron tratados durante un año y medio a dos años con ACTH. Se describe su progreso.

(2) Se conclude que presentemente la estimulación suprarrenal prolongada se justifica tan sólo en casos gravísimos.

(3) Se aclara y discute los problemas encontrados al controlar la terapia con ACTH.

(4) En un enfermo, al menos, se ha encontrado manifestaciones de disfunción suprarrenal; se las considera como complicaciones posibles de la estimulación suprarrenal prolongada.

STUDIES ON THE EFFECT OF PROBENECID ('BENEMID') IN GOUT

BY

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(RECEIVED FOR PUBLICATION FEBRUARY 10, 1954)

The discovery by Wollaston (1797) of uric acid in a gouty tophus, and the demonstration by Garrod (1848) that uric acid existed in excess amounts in the blood of gouty subjects, have not been followed as yet by any clear understanding of the precise relationship between this substance and the disease. In particular, the mechanism of production of the acute attack remains unexplained, and there exists a fascinating gap in our knowledge of the link between this striking clinical phenomenon and that relatively simple compound uric acid. Several reasons for this exist. Intervals between attacks may be as long as 62 years (Bauer, 1943), and it is therefore unusual to be able to observe the biochemical changes of an acute attack occurring fortuitously. Artificially induced attacks are unsatisfactory; high purine or high fat diets may themselves affect blood uric acid levels (Brøchner-Mortensen, 1939; Bauer, 1943; Bauer and Klemperer, 1947; Marson, 1953), and, although acute attacks have been observed after the administration and withdrawal of ACTH (Hellman, 1949; Levin and others, 1953), this substance has a uricosuric action (Forsham and others, 1946, 1948; Robinson and others, 1948; Gutman and Yü, 1950; Thorn and others, 1950; Wolfson and others, 1950), which renders interpretation difficult. Furthermore, the complete clinical remissions which characterize gout render the necessary in-patient observation during these periods difficult to achieve, and the tendency is for only those patients who have reached the chronic stage to accept this. Secondly, the classical severity of the acute paroxysm, so graphically referred to in the literature (*e.g.* by Sydenham, 1683; and, in more recent years, by Wood-Jones, 1948, 1950) renders it impossible to observe an untreated acute attack. Finally, the development of reliable and practical biochemical methods for the quantitative determination of uric acid in body fluids has proved difficult, and this is reflected in the massive literature on this problem. That adequate accuracy can be achieved, however, has been confirmed by the use of uricase (Blauch and Koch, 1939; Block and Geib, 1947), whereby the inaccuracy produced by non-uric acid chromogens can be excluded and measured. Buchanan and others (1945) have estimated that non-uric acid chromogenic material in the urine amounts to 60-90 mg./24 hrs, and Johnstone (1952), using a combination of the colour reagent of Brown (1945) and the uricase method of Block and Geib, found that they accounted for 7 mg./100 ml. in the urine and 0·2 mg./100 ml. in the plasma. There was no correlation between non-uric acid chromogens and uric acid, the former being within normal limits, and the difference between normal and gouty readings being due to uric acid. The only significant error from this source occurs in the presence of renal failure.

Many workers report that at least a proportion of gouty subjects show normal values in the blood, varying in different series from 7 to 28 per cent. (Cohen, 1936; Hench and others, 1928; Hill, 1938). An analysis of blood uric acid estimations on eight gouty subjects, when no drugs had been taken for 24 hours during periods of freedom from acute paroxysms, has been made on the material of a previous study (Mason, 1951), and this reveals that twelve readings (24 per cent.) out of 51 were below 4 mg. per cent. This figure agrees with those quoted of the proportion of cases of gout having a normal level. On the other hand, the relatives of gouty patients are not infrequently found to be suffering from asymptomatic hyperuricaemia (Talbott and Coombs, 1938a; Talbott, 1940, 1951). It is also recognized that hyperuricaemia due to renal failure is not associated with attacks of gout. Furthermore, the artificial production of gross hyperuricaemia by intravenous administration, even in gouty subjects, to over 20 mg. per cent. will not precipitate an attack (Folin and others, 1924).

Perhaps the greatest confusion lies in our understanding of the relationship of an acute attack to the level of circulating urate. The most important study in this connexion is that of Jacobson (1938), who makes the point that it is inherently impossible to obtain information from a study of individual cases and that only a statistical investigation will give the necessary evidence. He admits that his own data were obtained under conditions which only approximate to the ideal desiderata of frequent observations between and during attacks under controlled conditions of diet and medication. He was only able to detect significant differences between the readings obtained during asymptomatic and attack periods by comparing the observations during an arbitrary 3-day period before the attack with the remainder, and his findings suggested that the serum uric acid fell during the attack period.

Urinary uric acid estimations are subject to many of the same difficulties as blood studies; and, moreover, endogenous and exogenous uric acid may influence excretion independently (Brøchner-Mortensen, 1937). In addition, caffein, theophylline, and theobromine may be oxidized to methylated uric acid in the urine, and this may give a reaction to phosphotungstic acid. It is possible that the alleged uricosuric action of these substances is due to this effect (Buchanan and others, 1945).

It has been suggested that an acute paroxysm of gout may be associated with changes in uric acid excretion. Osler (Osler and McCrae, 1920) not only claimed that the blood uric acid is higher during an attack but that the output of uric acid is low during the intervals and rises at the onset. Talbott and others (1935) and Talbott and Coombs (1938b) describe a "gout cycle", in which a cyclic disturbance of electrolyte balance occurs in gouty subjects, but Levin and others (1953) were unable to confirm their findings.

Probenecid ("Benemid").—After the incidental finding that caronamide, had a uricosuric action (Wolfson and others, 1948), Boger and others (1950) showed that p-(di-n-propylsulphamyl)-benzoic acid (probenecid, "Benemid") had a similar and more potent effect, and appeared to be less toxic (Boger and Crosson, 1950). This substance is presumed to act by interference with renal tubular mechanisms, bringing about reabsorption of urate from glomerular fluid; its uricosuric action is well documented (Gutman and Yü, 1951; Talbott and others, 1951; Talbott, 1951), whilst its toxic effect on the kidney appears to be negligible (Sirota and others, 1952a, b). Of particular interest were the side-effects noted, which included the occurrence of acute attacks of gout in some cases. Gutman and Yü (1951) found, for example, that six of eighteen cases treated with probenecid 2 g. daily developed acute attacks within a few days. This substance, therefore, a potent and non-toxic uricosuric agent, provided an opportunity to study uric acid excretion and associated changes of blood levels in gouty subjects, and of the seven cases described in the present study, six had acute attacks whilst under investigation.

Methods

All patients except Case 3 were observed as in-patients. Free fluid intake was allowed without special dietary restrictions, except that patients were restricted to the standard hospital diet to the greatest practicable extent. The biochemical methods used are shown in Table I, the upper limit of normal being taken as 4 mg./100 ml. in the blood and 6 mg./100 ml. in the plasma or serum. Aspirin and other salicylates were excluded.

TABLE I

CLINICAL MATERIAL

Case No.	Sex	Age (yrs)	Duration of Gout (yrs)	Period of Study (days)	Method
1	M	59	27	32	*Blood:* Folin and Trimble (1924) *Urine:* Folin and Schaffer (Plimmer, 1918)
2	M	43	10	45	Bidmead (1951)
3	M	60	25	21	*Blood:* Folin and Trimble (1924) *Urine:* Folin and Schaffer (Plimmer, 1918)
4	M	43	23	11	Bidmead (1951)
5	M	52	3	13	Folin (1934)
6	M	56	15	86	Bidmead (1951)
7	M	46	5	7	*Blood:* Folin (1933) *Urine:* Benedict and Franke (1922)

Case Reports

Three illustrative cases are described and the findings in the other four cases are summarized.

Case 2, male, aged 43, had been found at the age of 21 to have albuminuria and was diagnosed as suffering from nephritis. He had been treated since then with a low protein diet, although albuminuria had persisted. His first attack of gout occurred in the big toe at the age of 33. At the age of 38 splenomegaly was noted and he was found to be anaemic. Despite much investigation in various countries the nature of his anaemia was never established. At the same time small tophi appeared on his ears. By the age of 40 his attacks of gout were affecting his hands and wrists, lasting from 2 to 3 weeks, with remissions of about the same length. Five months

before admission, tophi appeared on the left 2nd metacarpophalangeal joint, the left 5th proximal interphalangeal joint, and in both olecranon bursae. He had typical large tophi on both hands and elbows, with small tophi on both ears. His mucous membranes were pale and there were small glands in both axillae, the spleen being enlarged to a hand's breadth below the costal margin.

Haemoglobin 67 per cent.; red blood count 5,100,000 per c.mm.; colour index 0·66; white blood count 3,100 per c.mm.; differential count normal. No abnormal white cells were present.

Erythrocyte sedimentation rate 6 mm./hr (Wintrobe) uncorrected.

Urine fixed specific gravity of 1,006, with protein ++ but no abnormal cells or casts. Urea clearance (Van Slyke) 27 per cent. of maximum normal, blood urea 70 mg. per cent.

X rays of hands and feet showed marked punched-out erosions characteristic of gout.

This patient was studied for 45 days, a control period of 8 days, treatment with probenecid 1 g. daily for 19 days, and with 1·5 g. daily for 15 days. At the end of this period he was treated with 2 g. probenecid daily for 3 days only.

On the 7th day of his control period he developed a severe polyarticular attack of gout, the serum uric acid rising from 7·1 to 12·8 mg. per cent., and the blood urea from 70 to 105 mg. per cent. on the 10th day. He was therefore given colchicine 1/60 gr. 2-hrly for six doses, and probenecid 1 g. daily. Colchicine was continued after the initial loading dose in doses of 1/120 gr. three times a day for the rest of his period in hospital. The serum uric acid fell by the 15th day to 5·9 mg. per cent., the blood urea continuing to rise until the 14th day to 118 mg. per cent., and thereafter falling slowly to its previous level. On the 28th day after admission the dose of probenecid was increased to 1·5 g. daily, and tophectomy was carried out on the 36th day, both olecranon bursae being removed. During the course of treatment on the 18th day his renal function was reassessed, his urea clearance being 21·5 per cent. of maximum normal. Detailed figures are given in Table II and illustrated in Fig. 1 (opposite).

A striking feature of this case was the marked increase in the serum uric acid in association with the acute attack. However, the patient had a grossly deficient renal function and the blood urea was also rising during this period, and it is possible that the increasing serum uric acid is simply a reflection of renal failure. During the whole period of study an excess of uric acid amounting to 6,623 mg. was excreted. The tophi contained approximately 1,300 mg. uric acid, a relatively small amount in comparison with the excess excreted in the urine. This point is commented on below.

No definite conclusion can be made from this case as to the specific problem of the relationship of uric acid to the acute paroxysm of gout, for, although large changes in serum uric acid levels occurred at the time of the acute attack, the presence of renal failure with the rising blood urea complicates the picture to a degree which prevents the drawing of any conclusions relevant to this particular problem. However, with further experience in treating patients with probenecid it was confirmed that not infrequently an acute attack would develop during the first few days, at a time when the blood uric acid level had been brought to normal. This is illustrated in Case 5.

Case 5, male, aged 52 (Fig. 2, overleaf, and Table III, opposite), had his first attack of gout 3 years previously in one big toe, with a characteristic onset, and 6 months later he had had a similar attack in the right wrist, followed by other attacks. The present attack had developed 6 weeks previously in the right wrist. On admission there was swelling and extreme tenderness of both the right wrist and the right elbow. There were no tophi. At the outset of uric acid studies he was at the stage when an acute exacerbation of his attack was just settling, leaving him with considerable residual symptoms. During the 6-day control period his mean plasma uric acid was 6·6 mg. per cent. and his mean urinary uric acid output was 1,005 mg./24 hrs. On the 2nd day he was given colchicine in full doses, and subsequently 1/120 gr. twice daily. During probenecid administration the output of uric acid per 24 hours increased to 1,920 mg., and the total excess excreted was 5,490 mg. in 6 days. There was a fall in plasma uric acid levels from 6·2 mg. per cent. on the day before treatment to 4·0 mg. per cent. on the 4th day.

TABLE II

SERUM URIC ACID AND URINARY URIC ACID OBSERVATIONS IN CASE 2

Acute attack of gout occurred on Day 7, reaching maximum on Day 9. On Day 9 1/60 gr. colchicine was given 2-hrly for six doses, and thereafter 1/120 gr. three times daily. Tophectomy was carried out on Day 36.

Days	Urinary Volume (ml./24 hrs)	Urinary Uric Acid		Excess* Urinary Uric Acid (mg./24 hrs)	Serum Uric Acid (mg./100 ml.)	Blood Urea (mg./100 ml.)	Probenecid (g./24 hrs)
		(mg./100 ml.)	(mg./24 hrs)				
1– 8	1,509	35·4	532	—	9·3	84	—
9–27	1,467	45	656	+ 124	8·5	102	1
28–42	1,853	44·7	816	+ 284	8·4	64	1·5
43–45	2,235	24·5	560	+ 28	6·0	80	2

* Total excess excretion of urinary uric acid (37 days), 6,623 mg.

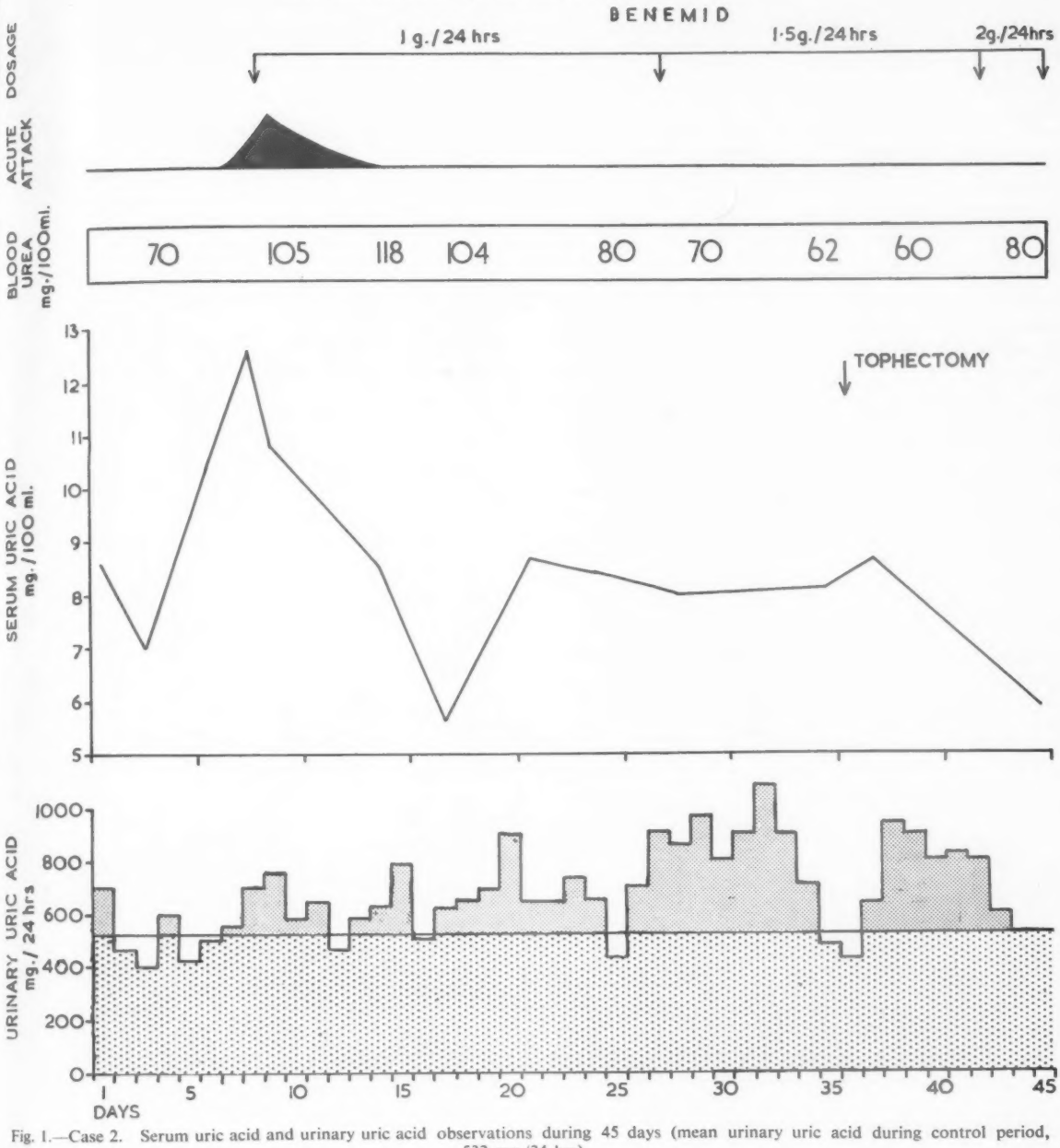

Fig. 1.—Case 2. Serum uric acid and urinary uric acid observations during 45 days (mean urinary uric acid during control period, 532 mg./24 hrs).

TABLE III

PLASMA URIC ACID AND URINARY URIC ACID OBSERVATIONS IN CASE 5

Days	Urinary Uric Acid (mg./24 hrs)	Excess† Urinary Uric Acid (mg./24 hrs)	Plasma Uric Acid (mg./100 ml.)	Dosage		Symptoms
				Colchicine (gr. 1/120/24 hrs)	Probenecid (g./24 hrs)	
1–6	1,005	—	6·6	2*	—	Settling
7–12	1,920	+ 915	4·2	2	2	Acute flare on days 9, 10 and 11

* On Day 1 colchicine was given to intolerance (1/120 gr. × 10).
† Total excess excretion of urinary uric acid (6 days), 5,490 mg.

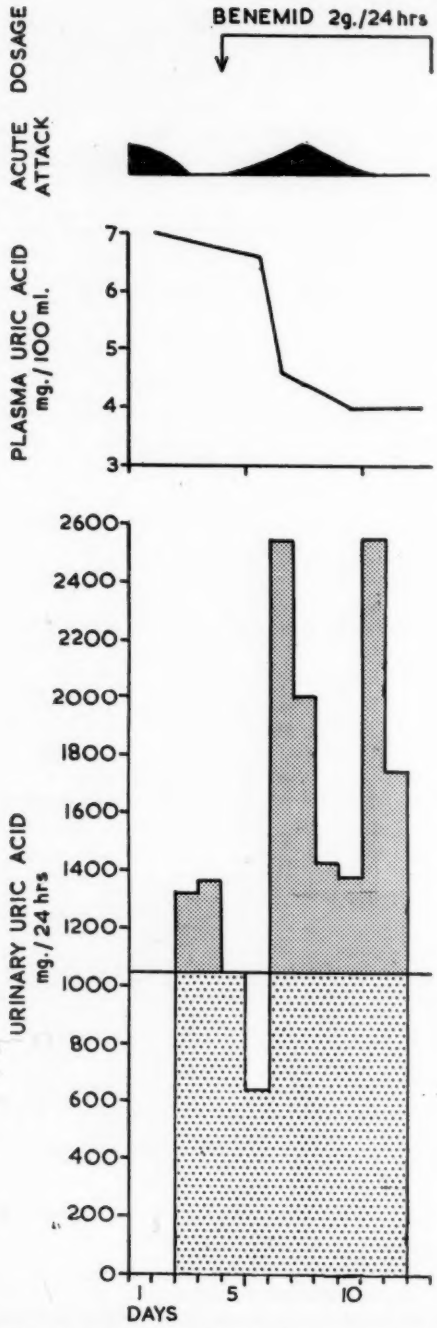

Fig. 2.—Case 5. Plasma uric acid and urinary uric acid observations during 12 days (mean urinary uric acid during control period, 1,005 mg./24 hrs).

On the 3rd day of treatment he had a definite acute flare in his wrist.

Case 6, male, aged 56 (Figs 3 and 4 and Table IV), was a severe case of gout with polyarticular attacks of long duration, his first attack having occurred 15 years previously. The knees, wrists, and fingers were involved, and he had developed tophi on both ears. He had been on a low protein diet for the previous 5 years. There was a strong family history. On examination small tophi were present in both ears, but, apart from minor degenerative changes in both knees and first metatarsophalangeal joints, his joints appeared normal.

Blood urea was 52 and 33 mg. per cent. on two occasions, and urea clearance (Van Slyke) 99 and 96 per cent. of average normal.

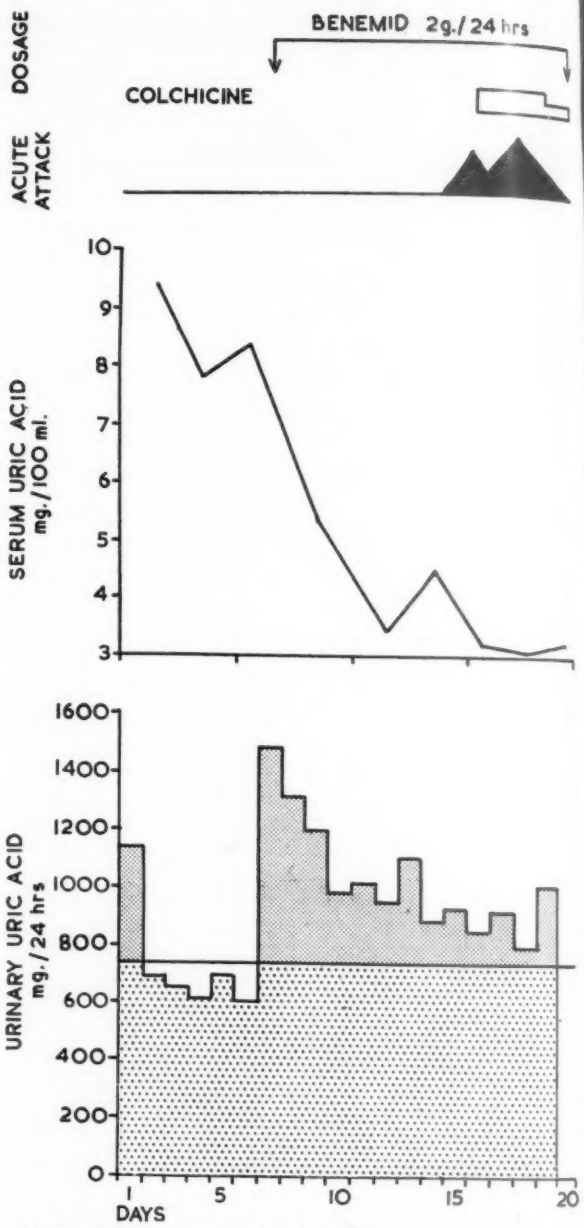

Fig. 3.—Case 6. Serum uric acid and urinary uric acid findings during 19 days' observation (mean urinary uric acid during control period, 745 mg./24 hrs).

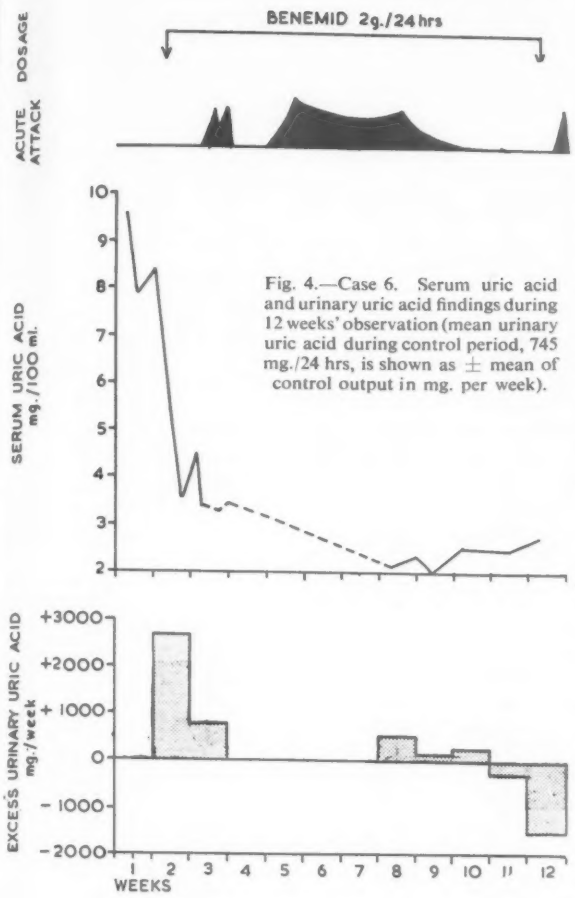

Fig. 4.—Case 6. Serum uric acid and urinary uric acid findings during 12 weeks' observation (mean urinary uric acid during control period, 745 mg./24 hrs, is shown as ± mean of control output in mg. per week).

Examination of material from a tophus showed crystals of sodium biurate with a positive murexide test.

X rays of the hands and feet showed small punched-out areas in both first metatarsophalangeal joints with osteo-arthritic changes.

During 15 days of therapy 3,563 mg. urinary uric acid was excreted over and above the anticipated excretion on the basis of control values. Serum uric acid fell quite rapidly from a maximum of 9·4 to 3·3 mg. per cent. on the 5th day of treatment. On Day 14 the patient developed an acute attack of gout in one big toe and on that day his serum uric acid was normal at 4·6 mg. per cent. On Day 17 a more intense attack developed and he took colchicine in full doses. The serum uric acid over this period was 3·4, 3·3, and 3·4 mg. per cent. He was discharged on the 22nd day on 2 g. probenecid daily. Within 24 hours of discharge he developed an intense polyarticular attack, but continued with probenecid, and colchicine 1/120 gr. four times daily. He was re-admitted 4 weeks after discharge, still with a very intense polyarticular attack. During the first week after admission (Days 52 to 58) he was still excreting a mean daily excess of 83·0 mg./24 hrs, and his serum uric acid was 2·2 and 2·3 mg. per cent. on two occasions. The attack gradually settled, and during the following 3 weeks the excretion of uric acid in the urine did not deviate by more than a few mg. from normal, the serum uric acid remaining at about the same level. He was treated briefly with phenylbutazone in the hopes of relieving his attack, but it is not possible to say whether this was effective. During the first 5-day period after discontinuing probenecid (Days 80 to 84), a total of 1,535 mg. uric acid was retained, and he had an acute attack of gout which was controlled with colchicine.

TABLE IV
SERUM URIC ACID AND URINARY URIC ACID OBSERVATIONS IN CASE 6

Days	Urinary Volume (ml./24 hrs)	Urinary Uric Acid (mg./100 ml.)	Urinary Uric Acid (mg./24 hrs)	Excess Urinary Uric Acid (mg./24 hrs)	Serum Uric Acid (mg./100 ml.)	Dosage: Colchicine (gr. 1/120/24 hrs)	Dosage: Probenecid (g./24 hrs)	Dosage: Phenylbutazone (mg./24 hrs)	Symptoms
1–6	3,177	23	745	—	8·6	—	—	—	Nil
7–13	2,764	40·6	1,134	+ 389	4·6	—	2	—	Nil
14–21	2,643	33	850	+ 105	3·7	7 (Day 17)	2	—	Acute monarticular attack
22–51	—	—	—	—	—	4	2	—	Severe polyarticular attack
52–58	1,998	42	828	+ 83	2·25	—	2	800 (Days 55-58)	Severe polyarticular attack
59–65	2,387	32·6	756	+ 11	2·1	—	2	800 (Days 59, 63, 64)	Attack settling
66–72	2,263	34·9	774	+ 29	2·5	—	2	200 (Days 67, 68)	Residual pain
73–79	2,407	30·6	709	− 36	2·5	—	2	—	Residual pain
80–84	1,811	23·4	438	− 307	2·9	8 (Day 84)	—	—	Acute monarticular attack

* Total excess excretion of urinary uric acid, Days 7-21, 3,563 mg.
† Estimated total excess uric acid excretion, Days 7-79, 7,953 mg.

TABLE V

SUMMARY OF FINDINGS IN CASES 1, 3, 4, AND 7

Case No.	Control Period			Probenecid (2 g./24 hrs)				Onset of Acute Attack (day of probenecid administration)
	Days	Serum Uric Acid (mg./100 ml.)	Urinary Uric Acid (mg./24 hrs)	Days	Serum Uric Acid (mg./100 ml.)	Urinary Uric Acid (mg./24 hrs)	Total Excess Urinary Uric Acid (mg.)	
1	10	6·9 (6)	329	13	4·5 (11)	494	2,245	—
3	9	7·1 (2)	275	11	3·4 (2)	486	2,321	6
4	4	9·0 (1)	680	7	4·9 (3)	911	1,617	5
7	2	*4·7 (2)	743	6	*3·4 (4)	1,226	2,417	2

Number of serum uric acid estimations given in brackets.
* Blood uric acid.

This case illustrates quite clearly that an attack of gout can occur when the serum uric acid levels have been brought to well below normal limits. The long-term studies here enable quantitative calculations to be made which are discussed below.

Cases 1, 3, 4, and 7.—These all gave essentially similar results, except that no acute attack occurred in Case 1. The findings are summarized in Table V.

Discussion

These investigations provided an opportunity of studying the relationship of uric acid to gout from two aspects:

(1) Relationship of the acute paroxysm of gout to blood levels,
(2) Quantitative studies.

Relationship of Acute Paroxysm of Gout to Blood Levels.—Cases 3, 4, 6, and 7 had acute attacks whilst under observation during probenecid therapy. Case 5 had an exacerbation of an acute attack, and Cases 2 and 4 developed an attack during the period of initial observation.

Case 3.—Unfortunately no observations of the blood levels were possible during the attack, which began on the 7th day of Benemid administration. Two days before this attack began, this patient's serum uric acid was 3·2 mg. per cent. compared with 6·6 and 7·6 mg. per cent. during the control period; 10 days after the attack began and 6 days after withdrawal of probenecid, the serum uric acid had risen to 7·4 mg. per cent. From the time of his last blood estimation to the height of the attack he excreted uric acid at a rate well above his mean control level (275 mg./24 hrs), a total excess of 478 mg., and he continued to excrete an excess throughout the period of probenecid administration. It seems probable, therefore, that his serum uric acid was normal during the attack.

Case 4.—This patient had two attacks during the 11 days of study. Again no blood estimation was carried out at the critical time, at the onset or at the height of the attack. On the 3rd day of his first attack (during the control period) his serum uric acid was 9 mg. per cent. On the day before his attack, during probenecid therapy, it was 4·6 mg. per cent., and on that and the succeeding two days he excreted a total excess of 1,500 mg. uric acid.

Case 6.—This case demonstrates very clearly the occurrence of an acute attack at a time when the level of circulating uric acid had been brought to normal. On re-admission a month later with a very severe polyarticular attack his serum uric acid had fallen still further to 2·2 and 2·3 mg./100 ml.

Case 7.—This case demonstrated a similar phenomenon. The blood uric acid during a 2-day control period was 4·4 and 5 mg. per cent., and at the height of his attack on the 4th day of probenecid therapy it had fallen to 2·7 mg. per cent. (Fig. 5, opposite).

Case 2.—This patient developed his acute attack during the control period, but the findings are of less value in this connexion in view of his gross renal failure. His serum uric acid rose rapidly from 8·6 and 7·1 to 10·4 mg./100 ml. on the day before the attack began, and reached a maximum of 12·8 mg. per cent. when probenecid administration was begun. His blood urea also rose from 70 to 96 mg./100 ml. on the 2nd day of his attack, 105 on the 4th day, and 118 on the 8th day. It may therefore be that the rising serum uric acid was associated with renal failure and it is difficult to draw any conclusions.

Case 5.—This patient had already developed an attack of gout when admitted, but on the 3rd day of probenecid administration he developed an acute exacerbation. His plasma uric acid had been 7 and 6·2 mg. per cent. during the control period. On the day before the exacerbation developed it was 4·6 mg. per cent., and on the 2nd day of the attack 4 mg. per cent.

It is evident that, whatever the changes in blood levels in a naturally occurring attack of gout, acute paroxysms can occur at a time when the level has been sharply brought to normal. This finding

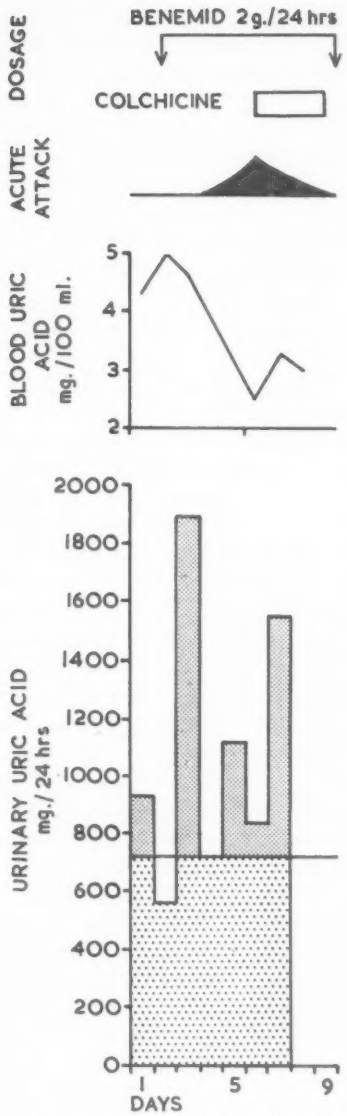

Fig. 5.—Case 7. Blood uric acid and urinary uric acid studies during 7 days (mean urinary uric acid during control period, 743 mg./24 hrs).

renders it difficult to believe that uric acid *per se* can be responsible for initiating the acute paroxysm of gout.

Quantitative Studies.—It is possible to compare the total excess of uric acid excreted with the change in plasma uric acid in Cases 1, 3, 4, 5, and 6. Case 2 is excluded because of the renal failure and the acute attack at the onset of treatment, and Case 7 is excluded because the estimations were made on whole blood. For convenience, the first 5 days of probenecid administration only are considered. As anticipated, the calculated loss of uric acid from the plasma is very much less than the excess excreted. Estimating the plasma volume at 0·05 body weight, the amount lost in 5 days of probenecid therapy is calculated as varying from 191 to 101 mg. (mean, 149 mg.). At the same time, the excess appearing in the urine over the same period lies between 4,755 and 768 mg. (mean, 2,136 mg.).

A similar, though smaller, discrepancy occurs if calculations are made on the uric acid contained in the extracellular fluid (0·2 body weight). On this basis, the loss of extracellular uric acid in these cases amounted to from 757 to 398 mg. (mean, 588 mg.). Table VI shows a similar analysis based on total body uric acid calculations. These are estimated on the assumption that uric acid is equally distributed throughout the body fluids (an assumption which is liable to serious objections which are discussed below), the total body fluid being estimated by the formula body water=0·7 body weight. On this basis the fall in calculated body urate varies between 2,645 and 1,393 mg. (mean, 2,173 mg.), whilst the excretion excess lies between 4,755 and 768 mg. (mean, 2,136 mg.). In all these cases, except Case 5, there was a discrepancy in the opposite direction, and previous quantitative studies of this nature have given essentially similar results. Graham (1920) also noted a similar discrepancy and concluded that the extra uric acid could not possibly have come from the blood alone, but might be accounted for in the amount distributed in solution in the tissue fluids. He was perhaps the first to draw attention to the possibility that uric acid in the solid phase might play a part. He also determined the total body uric acid on the assumption that it is equally distributed in the body fluids, assuming that water comprised 90 per cent. of the body weight. On this basis his patient had totals of 1,200 and 2,500 mg. uric acid on two occasions. In one experiment the estimated change in total body uric acid approxi-

TABLE VI

EFFECT OF 5 DAYS' PROBENECID ADMINISTRATION ON CALCULATED TOTAL BODY URIC ACID

Comparison with excess urinary excretion during the same period

Case No.	Weight (kg.)	Loss of Body Uric Acid (mg.)	Excess Urinary Uric Acid Excreted (mg.)	Discrepancy (urinary excess minus calculated change) (mg.)
1	93·2	2,778	1,455	− 1,323
3	66·8	1,558	768	− 790
4	85·9	2,645	1,480	− 1,165
5	90·5	1,393	4,755	+ 3,362
6	77·3	2,489	2,222	− 267
Mean	82·7	2,173	2,136	− 37

mated to the excess excreted, in another the decrease was greater than the excess excreted. One possible source of error to which he draws attention is that the flow of uric acid from the tissue fluids to the blood might require some time for equilibrium to develop, so that the concentration of uric acid in the plasma does not reflect the concentration of uric acid in the body fluids as a whole. Thus, calculations of total body uric acid on the basis of blood readings, even supposing the other assumption is correct, may be liable to serious error. The discrepancy here occurs (except for Case 5) in the same direction as Graham's, *i.e.* less uric acid was excreted in excess than the calculated body changes would account for. These discrepancies may well be due to the unreliability of calculations of body uric acid for the reasons given by Graham. Table VII shows similar calculations made in the same way on four non-gouty cases given 2 g. probenecid daily for 5 days. The response during this period shows no striking difference when compared with that of gouty subjects. The excess amount of uric acid appearing in the urine averaged 1,603 mg. as compared with 2,136 mg. in the gouty subjects, but it will be noted that the average body weight of the controls was 70·7 kg., and the gouty subjects weighed on the average 12 kg. (26 lb.) more. No differences in this respect could be detected which would be of use in differential diagnosis in individual cases, although it is possible that longer term studies might be of value.

In the one patient (Case 6) who was followed for a longer term, it is more probable that equilibrium is achieved. In this particular case a gap of 31 days occurred, however, when he was discharged from hospital, so that an approximation can only be made of the total excess uric acid excreted by assuming that it was at the rate of the mean of Weeks 3 and 8 (*i.e.* +94 mg./24 hrs). During Weeks 9, 10, and 11, the daily excretion reached a mean of +3·6 mg./24 hrs above the control values, which may be considered as within the experimental error. The total excess of uric acid excreted amounted to 7,953 mg., but the calculated change of body urate amounts to only 3,139 mg. There would appear to be a difference in this case as compared with the calculations based on short-term studies, since the excess of excretion over the calculated change in total body urate amounts to 4,814 mg. It seems likely that the long-term study gives a more reliable result. If one can accept, therefore, that in this case equilibrium had been achieved, the discrepancy found lends support to the hypothesis that uric acid in the solid phase is in equilibrium with body fluid urate. It is necessary to emphasize, however, that the urinary uric acid has had to be estimated over the period of one month, which must leave an element of doubt in this conclusion.

The above calculations may be compared with those made from injecting isotopic uric acid labelled in the 1 and 3 positions with N-15 (Benedict and others, 1949). The size of the pool in normal subjects was found to be about 1,200 mg., but in gouty subjects this was increased many times, sometimes fifteenfold, *e.g.* to 15,450 and 31,019 mg. (Benedict and others, 1950). The very size of the pool suggested that some at least of the uric acid must be in the solid phase. Benedict found very different figures for the concentration of uric acid in tissue fluids; in one case this amounted to 35·1 and 59·1 mg. per cent. These figures too are so high that solid uric acid deposits may well be involved.

Only in Case 6 was it possible to maintain the observations long enough to follow the urinary uric acid output until it reached approximately normal values. If we assume that uric acid deple-

TABLE VII

RESULTS OBTAINED IN FOUR CONTROL CASES GIVEN 2 g. PROBENECID DAILY FOR 5 DAYS

Calculated body uric acid changes correlated with observed urinary uric acid changes

Age (yrs)	Sex	Diagnosis	Weight (kg.)	Calculated Total Body Uric Acid			Excess Urinary Uric Acid (mg.)	Discrepancy (urinary excess minus calculated change) (mg.)
				Before Administration (mg.)	After Administration (mg.)	Change (mg.)		
44	M	Prolapsed intervertebral disk	65·0	2,457	955	−1,502	+2,040	+538
64	M	Prolapsed intervertebral disk	82·7	2,490	1,042	−1,448	+1,370	− 78
69	M	Rheumatoid arthritis	72·0	2,117	1,512	− 605	+1,350	+745
61	M	Osteoarthritis	63·2	1,591	442	−1,149	+1,650	+501
Mean			70·7	2,164	988	−1,176	+1,603	+427

tion had then occurred it is possible to calculate roughly the size of the miscible pool. The calculated total excess uric acid excreted amounted to 7,953 mg. uric acid in this case. This figure is of the same order as those of Benedict and others, and it is therefore possible that this patient's miscible pool was approximately this size. It must be borne in mind that the size of his remaining pool has not been calculated, a calculation which is possible in isotope dilution studies. In one gouty subject studied under similar conditions by Talbott (1951), using the isotope technique, a fall in pool size occurred as a result of probenecid administration from 2,205 to 1,622 mg., and in another (Bishop and others, 1951a, b) from 4,700 to 1,600 mg. These figures are of very much the same order as those in the present case.

Unfortunately in Case 2, which is the only other case in which a long-term study was possible, renal function was so impaired that uric acid depletion could not be obtained. Of particular interest in this case, however, was the carrying out of tophectomy on Day 36; it was after this operation that the serum uric acid fell from a mean of 8·2 mg. per cent. during the previous 10 days to 6 mg. per cent. a week after operation. The amount of uric acid in the tophi was surprisingly small, amounting to 1,330 mg. This suggests that either these tophi were not acting as "banks" partly included in the miscible pool, or that they had been depleted by treatment with probenecid. A total excess of 4,700 mg. uric acid had already been excreted at the time of operation. In view of the fact that Yü and Gutman (1951) have produced evidence that gouty tophi may be mobilized by prolonged use of probenecid, it is clearly possible that this had occurred when the tophectomy was carried out, and the smallness of the amount of uric acid in the tophus does not therefore exclude the possibility that uric acid in the solid phase is in equilibrium with that in solution.

Relationship of Uric Acid to Acute Attack.—In considering the relationship of uric acid and gout, we have to account for the fact that no consistent relationship can be established between uric acid levels and acute gout; furthermore, the present study suggests that attacks of gout may regularly occur when the blood level has been brought to normal by the use of probenecid.

It is difficult to avoid the conclusion that uric acid itself is not responsible for the acute attack of gout. If this is accepted, then one possible explanation is that a precursor of uric acid is involved. This precursor may theoretically be normal or abnormal, and there is very little data on which to decide between these possibilities. The possible intermediate products in the formation of uric acid have been recently reviewed by Gutman (1953). The answer to this problem may lie in the action of colchicine, for it is possible that colchicine acts by blocking the formation of this hypothetical precursor. If such is the case, then this must be an abnormal precursor, since colchicine has no effect on plasma uric acid level. There is some evidence, however, of another metabolic route in the formation of uric acid in gouty subjects: using labelled glycine in one case, Shemin and Rittenberg (1947) found that glycine can be responsible for the nitrogen in the 7 position in uric acid in man. Benedict and others (1952), using N-15 labelled glycine, were therefore able to identify the uric acid in the urine from this source, following the administration of isotopic glycine. Their findings suggested that in gouty subjects a more rapid mechanism exists for the transformation of glycine into uric acid than in normals, and they suggest that this may occur *via* a different metabolic route. Such a hypothesis would be consistent with the findings of the present investigation that acute attacks of gout may occur when probenecid administration has produced a uric acid diuresis and brought the blood levels to normal, for it is possible that by removing the end product of the metabolic chain the formation of precursors might even be increased. It would also be consistent with the observations of Wood-Jones (1950) and Barnett (1951), who suggest that the basis of the acute attack is a vasomotor disturbance; and there is no evidence that uric acid itself can in fact produce such an effect.

Summary

Observations are described of seven cases of gout treated with probenecid, urinary uric acid and blood uric acid estimations being carried out at the same time.

Attacks of acute gout were studied; these occurred at a time when the level of circulating urate had been brought to normal.

Attention is drawn to one possible explanation of this phenomenon: that not uric acid *per se* but a precursor may be responsible for the acute paroxysm. The use of a uricosuric agent, such as probenecid, has enabled quantitative studies to be made, which provide some evidence that uric acid in the solid phase is in equilibrium with uric acid in body fluids.

With the exception of Case 6, all the patients were under the care of Dr. W. S. C. Copeman, to whom I am greatly indebted, both for permission to study his cases and for his helpful advice.

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Etude de l'effet de *Probenecid ('Benemid')* sur la goutte

RÉSUMÉ

On présente les observations de sept cas de goutte traités par *probenecid*; au cours du traitement on determinait le taux de l'acide urique dans le sang et dans l'urine.

On étudia les attaques de goutte aiguë; ceux-ci survenaient alors que le taux de l'urate sanguin était ramené à la normale.

On attire l'attention sur une explication possible de ce phénomène: ce n'est pas l'acide urique lui-même, mais un précurseur qui serait responsable des paroxysmes aigus. L'emploi d'un agent uricosurique, tel que *probenecid*, a permis des études quantitatives indiquant que l'acide urique à sa phase solide se trouve en équilibre avec l'acide urique des liquides du corps.

Estudio del efecto de *Probenecid ('Benemid')* sobre la gota

SUMARIO

Se presentan observaciones de siete casos de gota tratados con *probenecid*; durante el tratamiento la tasa del ácido úrico en la sangre y en la orina fué determinada.

Se estudiaron ataques de gota aguda; estos ocurrían en los tiempos en que se normalizaba la tasa del urato sanguíneo.

Se llama la atención sobre una explicación posible de este fenómeno: que no el mismo ácido úrico sino un precursor sería responsable de los paroxismos agudos. El empleo de un agente uricosúrico, como *probenecid*, hizo posibles los estudios cantitativos indicando que el ácido úrico en su fase sólida está en equilibrio con el ácido úrico de los líquidos del cuerpo.

EFFECT OF POST-PARTUM PLASMA IN RHEUMATOID ARTHRITIS*

BY

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This report is a pilot study to determine the clinical effects of post-partum plasma in rheumatoid arthritis. After 1½ years of unsuccessful efforts to collect post-partum plasma through our obstetrical service on a voluntary basis, a grant of funds from the New York Chapter of the Arthritis and Rheumatism Foundation has made it possible to persuade donors to offer the necessary plasma.

Our observations are derived from a series of eleven patients with active rheumatoid arthritis who were given transfusions of post-partum plasma.

Material

The selection of cases for this report was based on the diagnostic criteria for active rheumatoid arthritis established by the American Rheumatism Association in the "Primer and Handbook for Arthritis Clinics" (Steinbrocker and others, 1949).

The ages of our eleven patients ranged from 29 to 59 years. There were seven females and four males. The average duration of the disease was 4·8 years, varying from 6 months to 15 years. All the patients selected for treatment had previously received physiotherapy and salicylates; five had previously been given Butazolidin, two chrysotherapy, two F alcohol, and three cortisone. Only one of the patients previously given steroid therapy had received any within 3 months of starting plasma.

Methods

The technique described by Granirer (1952) was followed meticulously. The only modification was the use of type-specific plasma, rather than pooled plasma, to obviate the possibility of reactions (Angrist, 1952; Hsia and others, 1953). Cross-matching was performed before each transfusion as an added precautionary measure.

Venous blood was obtained 12-48 hrs post-partum. All of the post-partum donors were on the obstetrical service of the Lenox Hill Hospital. When indicated, the red cells were returned intravenously to the donor.

The plasma was prepared in our blood bank in the routine manner. For precautionary measures it was deemed necessary to obtain two sterile cultures at 14-day intervals before the plasma was used.

Each patient was observed for a minimum period of 3 weeks, either in the hospital or in the out-patient clinic, before the initiation of our therapy.

The plasma was administered intravenously in doses of 250-275 ml. at weekly intervals for an arbitrarily selected course of 10 weeks.

To determine the clinical effects, a weekly appraisal of each patient was performed by two observers. Evaluation of each patient's progress included the routine assessment of four subjective factors:

(1) pain,
(2) stiffness,
(3) sense of well-being,
(4) joint tenderness.

Objective evaluation was based on the therapeutic criteria of the American Rheumatism Association (Steinbrocker and others, 1949). Radiographs of the affected joints were repeated when indicated. Temperature, pulse, and weight were recorded routinely.

Certain laboratory studies on each patient were repeated at bi-weekly intervals:

(1) Complete blood count and haemoglobin,
(2) Erythrocyte sedimentation rate,
(3) Total cholesterol and partition,
(4) Total serum proteins, albumin-globulin ratio, and circulating eosinophil counts.

Rose tests (SCA) were performed both before and after treatment.

* This study was aided by a grant from the N.Y. Chapter of the Arthritis and Rheumatism Foundation.

† Clinical Fellow by grant of the National Institute of Arthritis and Metabolic Diseases, United States Public Health Service.

Results

No consistent subjective or objective improvement was noted in any of these patients. Table I gives a summary of our results, including the number of transfusions of post-partum plasma, the stage of the disease, the sedimentation rate before and after therapy, the functional class before and after treatment, and the grade of response.

Eight patients completed the arbitrary course of ten transfusions. One patient obtained moderate subjective and objective benefit after the seventh treatment, but gradually worsened in spite of continuing therapy and an additional transfusion. After the eleventh post-partum plasma, plain blood plasma was introduced for 2 weeks without the patient's knowledge. Her condition continued to deteriorate, and she was started on oral Compound F alcohol and a moderate response soon followed.

In three patients, plasma therapy had to be discontinued after eight and nine transfusions, respectively, because of marked progression of the disease.

Two patients obtained some questionable subjective improvement that was not sustained.

Table II (opposite) shows the results of laboratory studies before and after treatment. There was no change in the level of the haemoglobin or other components of the blood picture. There was no improvement or trend toward restoration to normal in reversed albumin-globulin ratios. Blood sedimentation rates remained elevated and the values of cholesterol and its fractions were not significantly altered.

Untoward Effects.—Untoward effects were limited to transfusion reactions (Scudder, 1953). These were of three types:

(1) urticaria,
(2) rises in temperature,
(3) chills or chilly sensations with or without a rise in temperature.

Reactions usually developed soon after the transfusions; they were easily controlled by the usual measures, and in the cases of urticaria by antihistaminics. No instance of homologous serum jaundice has occurred so far, but many of the patients were not out of the potential incubation period at the time of writing.

Controls.—The complete lack of response to the post-partum plasma nullified the need for administering the control plasmas which were originally planned as part of the study.

Discussion

The observation that patients with active rheumatoid arthritis may experience a remission or show decided improvement during pregnancy has been confirmed by many investigators (Alfred-Brown, 1942; Sclater, 1943; Flynn, 1942; Hench, 1938; Holbrook, 1948). Hench (1938) reported a total of 37 cases of pregnancy in 22 patients with rheuma-

TABLE I

RESULTS OF ADMINISTERING POST-PARTUM PLASMA*

Case No.	Total Transfusions	E.S.R.†		Stage of Disease	Class		Grade Response	Comment
		Before Treatment	After Treatment		Before Treatment	After Treatment		
1	10	86	100	3	3	4	IV	Worse
2	11	48	37	2	2	3	IV	Worse. Now improved on Compound F
3	10	80	82	3	3	3	IV	Unchanged
4	10	53	57	2	3	3	IV	Slight subjective improvement
5	9	74	80	4	4	4	IV	Disease progressed Refused further treatment.
6	10	31	52	2	2	2	IV	Unchanged
7	10	90	82	2	2	2	IV	Unchanged
8	10	42	71	1	3	3	IV	Unchanged
9	8	74	80	1	2	4	IV	Worse
10	8	90	99	3	4	4	IV	Unchanged. Refused further treatment
11	10	43	40	2	2	2	IV	Unchanged

* According to the criteria of the American Rheumatism Association (Steinbrocker and others, 1949).
† Westergren (mm./hr).

TABLE II

ANALYSIS OF LABORATORY STUDIES BEFORE AND AFTER POST-PARTUM PLASMA

Case No.	Hgb (g.)		RBC (millions)		Total Cholesterol (mg./100 ml.)		Albumin (g./100 ml.)		Globulin (g./100 ml.)	
	Before	After	Before	After	Before	After	Before	After	Before	After
1	14·2	12	4·7	4·3	185	173	4·4	4·4	2·9	2·6
2	13·1	12·4	4·4	4·2	176	171	3·5	3·7	3·6	3·6
3	10·2	12·1	3·4	4·2	225	219	3·0	3·3	5·7	5·9
4	15·5	13·3	4·7	4·6	235	212	3·8	2·4	4·2	5·4
5	10	10	3·6	3·8	151	137	3·0	3·2	3·3	3·8
6	12	11·9	3·7	4·0	170	192	4·0	4·6	3·3	3·9
7	13	13·8	4·2	4·6	163	180	5·2	5	1·9	2
8	12·6	12·1	4·6	4·7	152	156	2·9	3·7	2·9	3·9
9	12·5	12·8	4·1	4·2	180	170	5·2	5	2·9	2·7
10	10·4	8·4	3·8	3·4	160	146	3·0	4·4	2·5	4·8
11	11·9	13·1	4·2	4·6	161	150	3·5	3·8	3·9	3·9

toid arthritis. There was marked improvement during 34 (91 per cent.) of their pregnancies. Holbrook was able to collect a total of 96 pregnancies in women with active rheumatoid arthritis; eighty (83 per cent.) showed marked improvement or developed a remission during gestation. With this relationship in mind various ingenious methods of reproducing the effects of pregnancy have been devised. It is convenient to divide the methods into two categories:

(1) Direct influence of pregnancy,
(2) Indirect effect through products of pregnancy.

Direct Effect.—Pregnancy *per se* has been advised by some as a therapeutic aid (Holbrook, 1948), but needless to say this is not always practicable.

An attempt at producing a state of "pseudo-pregnancy" with massive doses of human chorionic hormone in a patient with rheumatoid arthritis was reported by Archer (1950), but pseudo-pregnancy was not achieved and no clinical benefit resulted.

We were unable to uncover any report in the literature describing the effect upon rheumatoid arthritis in patients developing pseudo-cyesis.

Indirect Effect.—The indirect effect through pregnancy-products is the more practical and is the one with which we are chiefly concerned. The current interest in the use of pregnancy blood and its derivatives was initiated by Barsi in 1941; 6 years later (Barsi, 1947) he reported a study of 28 patients and described beneficial results in 64 per cent., with no change in 36 per cent. of his series. He felt the results were not statistically significant, but was impressed with the rapidity of improvement and the lasting effects in those patients favourably affected.

Since that time other workers have reported the use of pregnancy blood, post-partum plasma, and placental cord serum.

Table III (overleaf) summarizes ten analytical studies with pregnancy products reported in the literature.

Lucherini and Pala (1951) reported four patients with rheumatoid arthritis given eight transfusions of 300 ml. pregnancy blood. Two patients were unchanged; improvement was reported as moderate in one, and good in another.

Holbrook (1951) noted two or three dramatic results in a series of over one hundred cases treated by pregnancy blood, but discontinued the treatment because there was not enough pregnancy blood available.

Four independent investigators reported varying results with placental cord serum. Tufts and others (1950) reported beneficial results with placental cord serum given in combination with sodium salicylate in eight cases of rheumatoid arthritis.

Aronson and others (1952) and Levy and others (1953) reported favourably on a total series of 47 cases of rheumatoid arthritis treated with placental cord serum, 10 ml. intramuscularly twice weekly. Although no patient gave a Grade I response, 31 (66 per cent.) had a Grade II response.

Spielberg (1953) reported fifteen cases treated with placental blood serum; three achieved a Grade I response, and another three had a Grade II response.

Simson and Bunim (1952) reported a series of

TABLE III
HISTORY OF PREGNANCY PRODUCTS USED IN RHEUMATOID ARTHRITIS

Analytical Investigations		Agent	No. of Cases	Results (Grade Response)*				Authors' Opinion
Author	Date			I	II	III	IV	
Barsi	1947	Pregnancy blood	28					Beneficial results 64 per cent. Rapid and lasting effect No change 36 per cent.
Lucherini and Pala	1951	Pregnancy blood	4					One good improvement One moderate improvement Two unchanged
Tufts and others	1950	Placental cord serum (with Na salicylate)	9					Beneficial
Aronson and others	1952	Placental cord serum	47	0	31 (66%)	10 (21%)	6 (13%)	Very encouraging
Levy and others	1953							
Spielberg	1953	Placental cord serum	15	3 (20%)	3 (20%)	4 (27%)	5 (33%)	Valuable
Simson and Bunim	1952	Placental cord serum	8			2	6	No significant beneficial effect
Granirer	1951	Post-partum plasma	8		8			Remissions in all. Seven additional patients unresponsive to steroids improved with post-partum plasma
Norcross and Lockie	1951	Post-partum plasma	6					No subjective or objective improvement
Neustadt and others (Present study)	1954	Post-partum plasma	11				11	No significant response Four patients worse

* Steinbrocker and others (1949).

eight patients treated with injections of placental serum, in whom no significant beneficial effect was obtained.

Granirer (1951) reported the successful use of post-partum plasma in eight patients with rheumatoid arthritis. In this study he stated that all his patients sustained gradual remissions lasting from 6 weeks to 1½ years. Chemical abnormalities of the blood, such as anaemia and reversal of the albumin/globulin ratio, were restored to normal. However, the blood sedimentation rate did not improve. No beneficial response was obtained when plain plasma was administered to a control group of patients.

Norcross and Lockie (1951) administered 250 ml. post-partum plasma once a week for a period of 12 weeks to six patients with active rheumatoid arthritis. No subjective or objective improvement was obtained.

Bunim (1951) mentioned two patients who failed to respond to sixteen post-partum transfusions, but showed moderate improvement when a steroid compound was administered.

Hsia and others (1953) recently reported the administration of Cohn's Fraction IV prepared from pooled post-partum plasma to a total of sixteen children, seven with rheumatoid arthritis. No beneficial effect on the rheumatoid arthritis was observed, and four out of the sixteen patients treated developed homologous serum hepatitis.

Although our series consists of only eleven patients, for the purposes of a screening study of the effects of post-partum plasma, we feel this material is adequate to reflect at least the trend of responsiveness, since the original report on this subject was based on only eight cases, and no further analysis of results in a larger group has appeared to our knowledge. Moreover, it has been stated by Granirer that improvement usually occurs between the fourth and sixth treatment, and all but one of the patients in this series have received eight or more transfusions of the specific plasma.

Plain Blood and Plasma Transfusions.—Some investigation of the use of normal blood and plasma in the treatment of rheumatoid arthritis has also been pursued. Repeated transfusions of normal blood have been recommended in patients with relatively acute or subacute rheumatoid arthritis. After the transfusions some striking remissions of the disease have been described by some observers (Holbrook, 1951).

Simpson and others (1949) treated forty patients with rheumatoid arthritis with blood transfusions, and ten patients with plasma transfusions. An immediate improvement in levels of haemoglobin, haematocrit, and blood sedimentation rate occurred in all patients given whole blood. However, these constituents returned to their previous abnormal

values within 28 days. Patients given plasma showed no improvement in these estimations. The arthritis was reported to be unaffected by the transfusions.

Summary

(1) The clinical and certain haematological and biochemical effects produced by the intravenous administration of 250 ml. post-partum plasma once a week for 8 weeks were observed in a series of eleven patients with active rheumatoid arthritis.

(2) This study has failed to demonstrate any significant responsive trend or any appreciable beneficial effect of post-partum plasma on the symptoms or course of active rheumatoid arthritis.

(3) No significant influence on abnormal blood chemical constituents was observed in any of our group during or after the administration of post-partum plasma.

(4) The administration of post-partum plasma as a therapeutic measure for rheumatoid arthritis in our small series demonstrated no evidence of benefit to justify its further investigation.

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Effet du plasma puerpéral sur l'arthrite rhumatismale

RÉSUMÉ

(1) On observa les effets cliniques et certains effets hématologiques et biochimiques produits par l'administration intraveineuse de 250 cc. de plasma puerpéral une fois par semaine à un groupe de onze malades atteints d'arthrite rhumatismale.

(2) Au cours de cette expérience on ne put déceler aucune tendance à une réponse significative ni aucun effet salutaire appréciable du plasma puerpéral sur les symptômes ou l'évolution de l'arthrite rhumatismale active.

(3) Pendant ou après l'administration du plasma puerpéral on n'observa dans aucun cas un effet significatif sur les composants chimiques anormaux du sang.

(4) Dans notre petite série l'administration à titre thérapeutique du plasma puerpéral dans l'arthrite rhumatismale n'offrit aucune indication favorable qui puisse justifier des recherches ultérieures.

Efecto del plasma puerperal sobre la artritis reumatoide

SUMARIO

(1) Se observó los efectos clínicos y algunos efectos hematológicos y bioquímicos consecuentes a la administracion endovenosa de 250 cc. de plasma puerperal una vez por semana a un grupo de once enfermos con artritis reumatoide.

(2) No fué posible demostrar en este estudio tendencia alguna a una respuesta significativa ni efecto beneficioso apreciable del plasma puerperal sobre los síntomas o la evolución de la artritis reumatoide activa.

(3) Durante o después de la administración del plasma puerperal en ningún caso se vió un efecto significativo sobre los componentes químicos anormales de la sangre.

(4) En nuestra pequeña serie la administración de plasma puerperal como medida terapéutica en la artritis reumatoide no evidenció ventaja alguna que pudiera justificar investigaciones ulteriores.

THE ARTERITIS OF RHEUMATOID ARTHRITIS

BY

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The occurrence of vascular lesions in rheumatoid arthritis has been recognized for some time, but interest in them has been of a sporadic nature until recently. In the last few years American workers have published more detailed studies of arteritis in skeletal muscles, subcutaneous nodules, and synovial tissue (Sokoloff and others, 1951, 1953). Sokoloff and his colleagues regarded the lesion in the muscles as specific, but this has been questioned by other workers (Bauer, 1950; Rinehart, 1950). The arteritis has usually been subacute, but some observers have described appearances like those of polyarteritis nodosa (Graef and others, 1949; Case Records of the Massachusetts General Hospital, 1951), and occasionally an association has been noted between such lesions and treatment with ACTH or cortisone (Levin and others, 1953). At the meeting of the American Rheumatism Association in 1953, four workers or groups of workers referred to cases of generalized arteritis in rheumatoid arthritis, and this was frequently associated with hormone therapy (Robinson and others, 1953 and subsequent discussion). Arteritis was not described in the viscera in thirty fatal cases reported before the introduction of ACTH and cortisone (Baggenstoss and Rosenberg, 1943). Less interest has been shown in the vascular lesions of rheumatoid arthritis in Great Britain, though reference has been made to arterial lesions in nodules (Collins, 1937), muscles and nerves (Cruickshank, 1952), and the heart and kidney (Ellman and Ball, 1948), and to the occurrence of polyarteritis nodosa complicating hormone therapy (West and Newns, 1953).

No attempt has yet been made to correlate the arteritis found in muscles, nerves, and elsewhere with the cardiac lesions found in fatal cases. It is the object of this paper to present such a study in 72 cases of the disease. It will be demonstrated that

TABLE I
TISSUES STUDIED, SHOWING DISEASE OF PATIENT AND SITE OF TISSUE

Disease	Total Patients	No. of Patients from whom Various Tissues were Studied					
		Heart	Synovial Tissue	Muscle	Nerve	Subcutaneous Nodule	Viscera
Rheumatoid Arthritis {Autopsy	72	72	32	26	21	5	69
Rheumatoid Arthritis {Biopsy	133		36	68		44	1 spleen
Ankylosing Spondylitis	17	5	8	10	2		5
Osteo-Arthritis	33		27	9	1		3
Gout	4	4	2	2	1	2	2
Rheumatic Fever {Active	57	49	9	13	1	6	49
Rheumatic Fever {Healed	196	199		15	7		170
Subacute Bacterial Endocarditis	27	23	2	4	1		22
Systemic Lupus Erythematosus	14	14	8	9	9		14
Polyarteritis Nodosa	31	31	4	16	10	3	29
Dermatomyositis	7	1		7			2
Scleroderma	7	4	1	7			4
Henoch-Schönlein Purpura	3	Skin lesions from three cases. Muscle lesions from one case					
Temporal Arteritis	6	Temporal and/or occipital arteries from six cases					
Granuloma Annulare	11	Cutaneous lesions from nine cases. Subcutaneous lesions from two cases					

arteritis occurs both in the heart and in other situations in an appreciable proportion of cases, and that some of the cardiac lesions hitherto interpreted as evidence of rheumatic heart disease can be regarded as part of the pathology of rheumatoid arthritis.

Material

Tissues were obtained at autopsy in 72 cases of rheumatoid arthritis (Table I). Blocks were taken from the heart, synovial tissue, muscle, nerve, and nodule in only three cases, from four of these tissues in fourteen cases, from three tissues in five cases, from two tissues in seventeen cases, and from the heart alone in 33 cases. In 43 instances, multiple blocks were taken from the heart, using the technique of Gross and others (1930), and multiple blocks were usually taken from synovial tissue, muscle, and nerve when these were examined. As a rule, single sections stained with haematoxylin and eosin were examined, but extra stains or serial sections were occasionally used. This autopsy material was compared with specimens obtained at biopsy from 133 cases of rheumatoid arthritis, and with both autopsy and biopsy material from 413 other cases of rheumatic and vascular disease, as indicated in Table I.

Results

Arteritis, or evidence of previous arteritis, was found in eighteen of the 72 cases of rheumatoid arthritis coming to autopsy. These cases have been divided into two groups, according to whether evidence of rheumatic heart disease was present or not. The lesions accepted as indicating rheumatic heart disease were myocardial Aschoff bodies, active or healed valvulitis, and active or healed left auricular endocarditis.

Group I. Cases with Evidence of Rheumatic Heart Disease.—Seven cases fell into this group. The anatomical distribution of the lesions and certain other information about the patients is presented in Table II. The patients were mostly elderly (average age 70) with inactive arthritis of considerable duration. A previous history of rheumatic fever was obtained in only two cases. The only patient under 50 years of age in the group (Case 10) had inactive rheumatoid arthritis of short duration but was found to have active rheumatic carditis at autopsy. The vascular lesions in the heart were

TABLE II

CASES OF RHEUMATOID ARTHRITIS WITH RHEUMATIC HEART DISEASE (Group I)

Case No.	Sex	Age (yrs)	Duration of Rheumatoid Arthritis (yrs)	Clinical Activity of Rheumatoid Arthritis at Death	Pathological Findings							History of Rheumatic Fever
					Heart		Other Sites of Arteritis					
					Cardiac Arteritis	Other Lesions	Synovial Tissue	Muscle	Nerve	Subcutaneous Nodule	Viscera	
4	F	82	5	–	Posterior papillary muscle	Adherent pericardium Mitral stenosis Aortic fibrosis		0		+	0	0
7	F	82	6	–	Left ventricle	Pericardial fibrosis Mitral stenosis	0	0	0		0	Childhood
10	M	48	1½	–	Posterior papillary muscle	Adherent pericardium Active myocarditis Active valvulitis	0	0	0		0	Active at death
11	F	82	?	–	0	Mitral stenosis Aortic fibrosis	0	0	+		0	0
15	F	72	Many	–	Left ventricle	Pericardial fibrosis Mitral fibrosis Aortic fibrosis	0			0	0	0
16	F	?	Many	–	Left ventricle	Pericardial fibrosis Mitral fibrosis Aortic fibrosis					0	0
18	M	56	10	+	Left ventricle	Pericardial fibrosis Mitral stenosis Aortic fibrosis	0	0			0	32-36 yrs before death
Number with Arteritis					6		0	0	1	1	0	

confined to the left ventricular myocardium. In six of the cases the lesions were of old standing and inactive (Fig. 1), and in the seventh (Case 10) subacute arteritis accompanied the active rheumatic carditis (Figs 2 and 3). Arteritis was seen outside the heart in Case 11 only—in one of three blocks of femoral nerve. The appearances were of a healing subacute arteritis associated with thrombosis (Fig. 4).

Group II. Cases without Evidence of Rheumatic Heart Disease.—Group II contains eleven cases of younger average age (58) than Group I, and the rheumatoid process was active at death in half of them although of longer duration than in Group I (Table III). Cardiac lesions other than arteritis were present in six cases, but cannot be regarded as indicative of rheumatic heart disease. The pericarditis in Case 17 and the myocarditis in Cases 2, 8, 9, and 17 were all non-specific. The endocardial lesions in the mitral ring and valve of Case 1 were those of "rheumatoid" endocarditis (Baggenstoss and Rosenberg, 1944). Calcareous aortic stenosis, which was present in Case 17, is included in this group because of the doubt about its rheumatic basis (Clawson and others, 1938; Sohval and Gross, 1936; Karsner and Koletsky, 1947; Hultgren, 1948).

The vascular lesions in the heart were usually seen in small arteries. They were usually found in only one of the blocks studied. The most florid changes were seen in Case 8 in the form of infiltration of all coats of the vessel with round cells (Fig. 5, overleaf). This was most marked in the adventitia where lymphocytes predominated, whereas in the other coats the infiltrating cells were less numerous and were mostly histiocytes. The internal elastic lamina showed several defects (Fig. 6, overleaf), but no wholesale necrosis of tissue such as occurs in polyarteritis nodosa. The media was oedematous and both it and the intima were thickened by fibrosis. This had caused narrowing of the lumen but there was no thrombosis. Another vessel in this heart showed a later stage in the process with much fibrosis of the media, complete destruction of elastic tissue, and an organizing thrombus in the lumen. Healing arteritis was seen in several epicardial vessels in Case 17, in the form of fibrosis with distortion of the media where muscle but not elastic tissue had been lost (Fig. 7, overleaf). The remains of round-cell infiltration was seen in and

TABLE III

CASES OF RHEUMATOID ARTHRITIS WITHOUT RHEUMATIC HEART DISEASE (Group II)

Case No.	Sex	Age (yrs)	Duration of Rheumatoid Arthritis (yrs)	Clinical Activity of Rheumatoid Arthritis at Death	Pathological Findings						
					Heart		Other Sites of Arteritis				
					Cardiac Arteritis	Other Lesions	Synovial Tissue	Muscle	Nerve	Subcutaneous Nodule	Viscera
1	F	74	9	+	Left ventricle and mitral valve	Rheumatoid endocarditis	0	0	0		0
2	M	63	10	+	Left ventricle	Adherent pericardium Myocarditis	0	0	+		Trachea
3	M	71	4	–	Left ventricle	0		0	+		0
5	F	63	32	–	0	0	0	0	+	0	0
6	F	32	4	+	Posterior papillary muscle	Myocarditis Infarcts	0	0	+		0
8	M	54	32	+	Right atrium and epicardium	0	0	+	+		Oesophagus
9	M	49	2½	+	0	Myocarditis	0	+	0	0	0
12	F	82	Many	–	Posterior papillary muscle	0	0	0	0		0
13	F	57	21	+	Left ventricle	Pericardial fibrosis 0	0	+	0		0
14	F	54	8	–	Interventricular septum	0	+				0
17	F	68	3	–	Epicardium	Subacute pericarditis Myocarditis Calcareous aortic stenosis					Breast, Pancreas (Periosteum)
Number with Arteritis					9		1	3	5	0	3

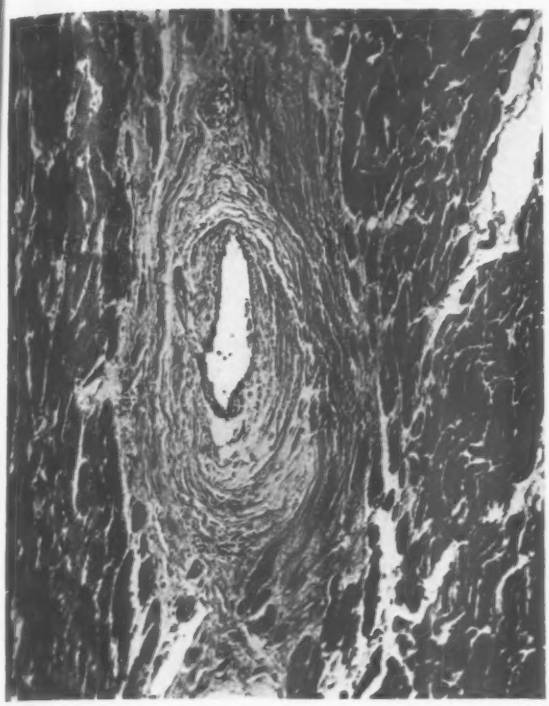

Fig. 1.—Case 18, left ventricle. Healed arteritis and periarterial fibrosis, minimal atheroma present in main coronary arteries. Haematoxylin and eosin. × 100.

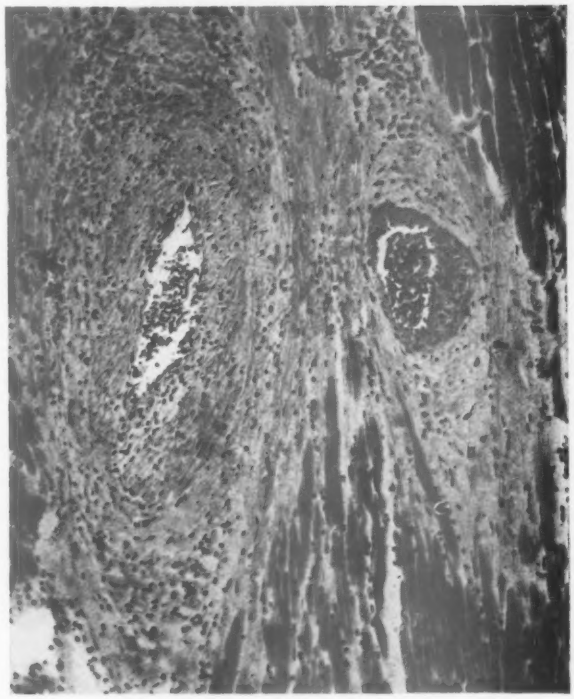

Fig. 3.—Case 10, posterior papillary muscle. Subacute arteritis with much fibrosis of vessel walls and adjacent tissue. Haematoxylin and eosin. × 100.

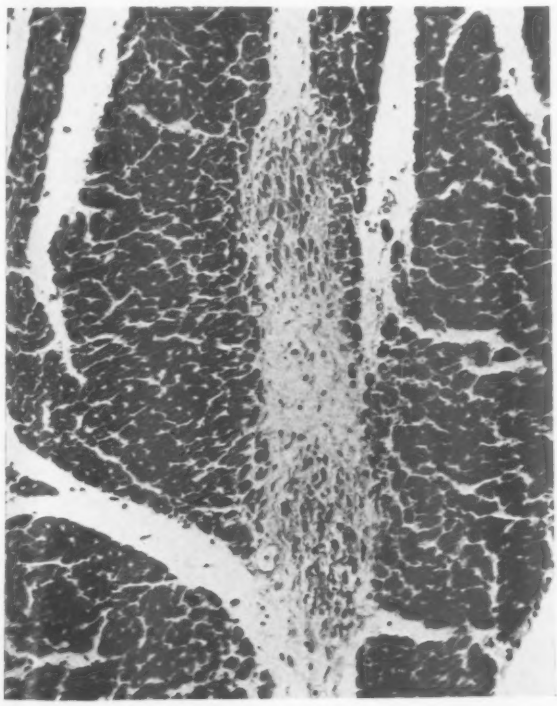

Fig. 2.—Case 10, interventricular septum. Two fully-developed Aschoff bodies lie close together in a small septum. Haematoxylin and eosin. × 100.

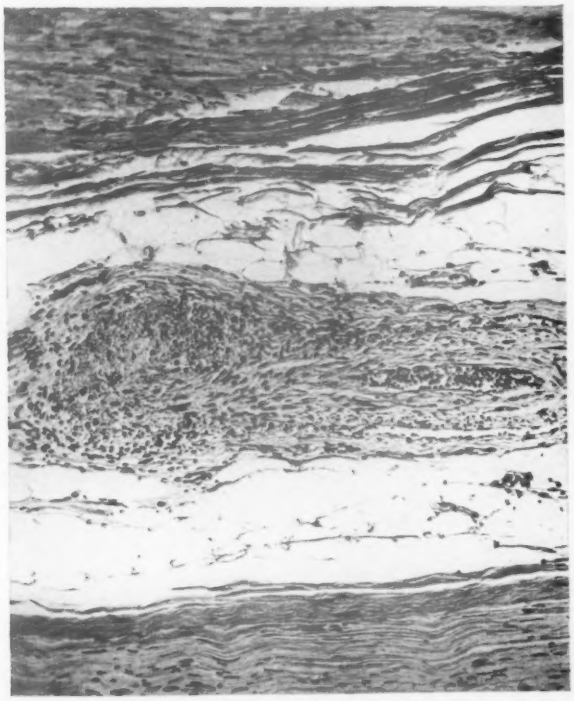

Fig. 4.—Case 11, femoral nerve. Subacute arteritis with thrombosis. Haematoxylin and eosin. × 100.

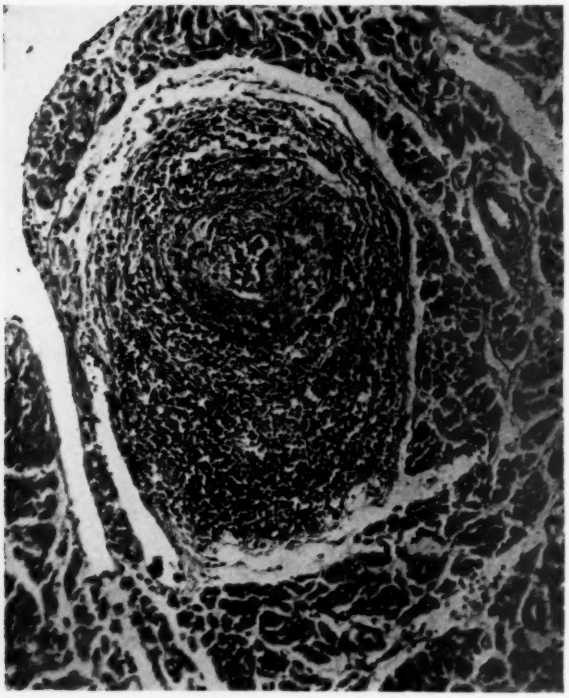

Fig. 5.—Case 8, right auricle. Intense subacute arteritis affecting all coats. Haematoxylin and eosin. × 100.

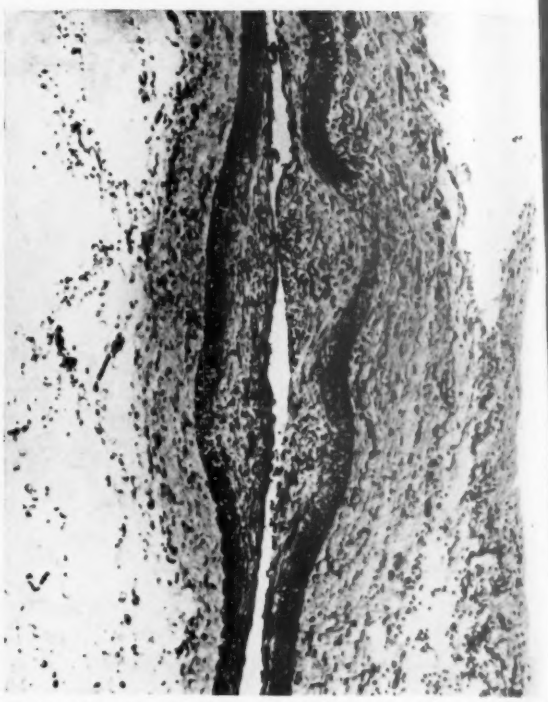

Fig. 7.—Case 17, epicardium of right ventricle. Healing subacute arteritis with loss of medial tissue. Haematoxylin and eosin. × 50.

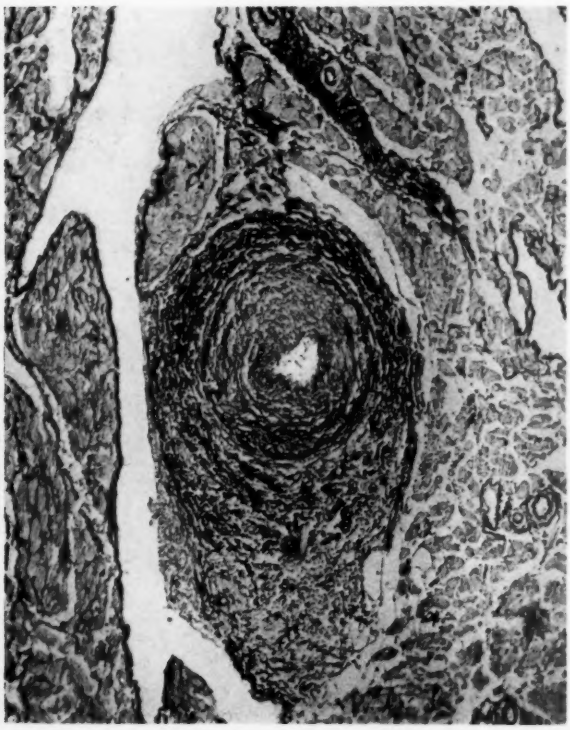

Fig. 6.—Case 8, same vessel as in Fig. 5, showing patchy destruction of elastic tissue. Weigert's elastic tissue stain. × 100.

Fig. 8.—Case 6, posterior papillary muscle. Healed arteritis and periarterial fibrosis, no atheroma in main coronary arteries. Haematoxylin and eosin. × 40.

around the affected vessels and generalized infiltration with such cells occurred in the outer part of the epicardium. In five other cases (1, 6, 12, 13, and 14) only healed lesions were detected—intimal fibrosis with variable loss of elastic tissue and disruption of the media with fibrosis (Fig. 8). These lesions were accompanied by many small organizing infarcts in Case 6. A peculiar focal accumulation of lymphocytes and histiocytes was seen in the media and adventitia in an artery in the right ventricle in Case 3. This was accompanied by some distortion of the vessel wall but no necrosis was seen (Fig. 9). Involvement of arterioles was seen only in Case 2 where arteriolonecrosis accompanied a diffuse non-specific subacute myocarditis of the left ventricle.

The vascular lesions in the other tissues were again present in only a few of the blocks studied. Thus in synovial tissue at least three blocks were taken, yet only a single lesion was found; an average of seven blocks of muscle and eight of nerve were taken, and lesions were found usually in only one block of muscle and two of nerve. Most of the changes seen covered the same range as in the heart. In some cases they were of the same degree and stage as the lesions in the heart (Cases 6 and 8). In others there were decided differences between cardiac and extracardiac lesions. Thus in Case 2 the tracheal and nerve lesions affected small arteries and were at a more advanced stage than in the heart (Fig. 10; and see Cruickshank, 1952, Fig. 19), and in Case 13 active arteritis was seen in nerve, whereas the cardiac lesion was healed. In Case 8, the arteritis in muscle and nerve was subacute as in the heart (see Cruickshank, 1952, Figs 17 and 18), but in the oesophagus a smaller vessel showed more recent necrosis accompanied by round-cell infiltration (Fig. 11, overleaf). Acute necrotizing arteritis affecting a larger vessel was seen in a nodule in the breast in Case 17 (Fig. 12, overleaf). The neighbouring breast tissue showed cystic hyperplasia. The lesions in the pancreas and sternal periosteum of this case were similar to those already described in the heart. Vascular lesions were seen twice in nodules, once in a small artery in the peripheral zone of an established nodule where an obliterative lesion had developed (Case 4, Fig. 13, overleaf), and once in relation to arterioles in a biopsy from a case of juvenile rheumatoid arthritis (Fig. 14, overleaf).

No vascular lesions were seen in other situations

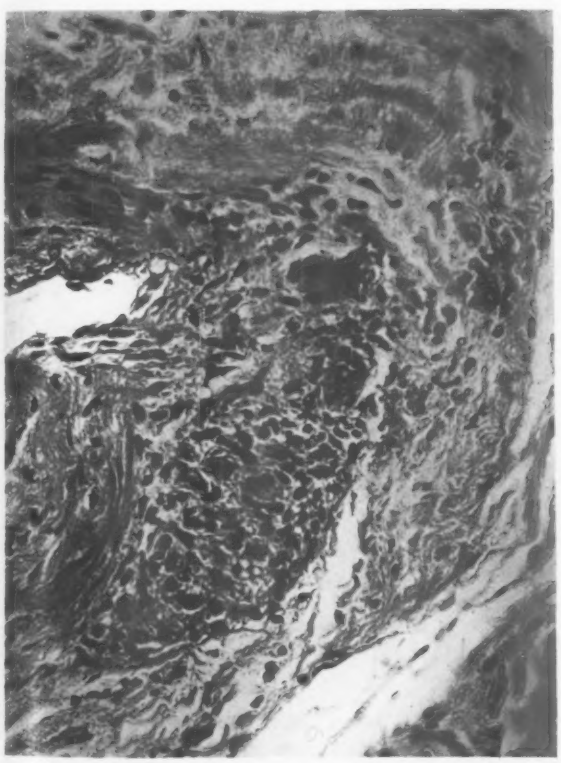

Fig. 9.—Case 3, right ventricle. Focal accumulation of lymphocytes and histiocytes in moderate-sized artery, minimal atheroma present in main vessels. Haematoxylin and eosin. × 100.

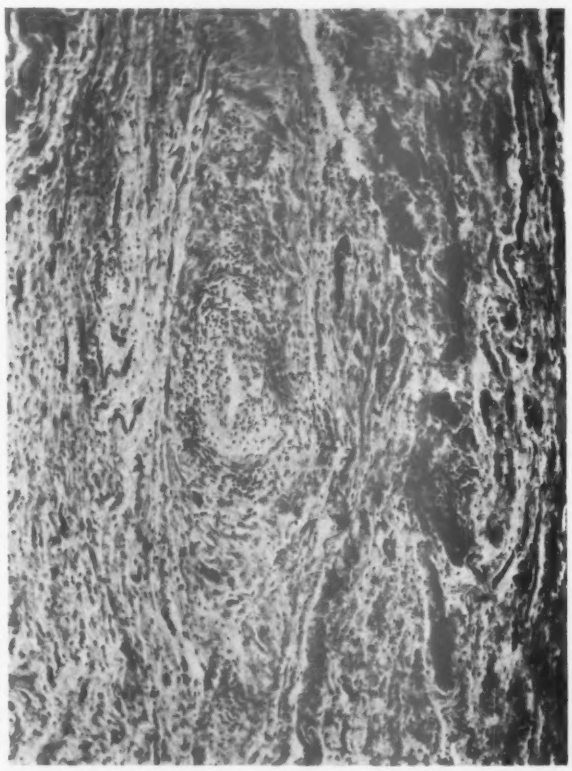

Fig. 10.—Case 2, fibrous nodule between trachea and oesophagus. Healing subacute arteritis. Haematoxylin and eosin. × 50.

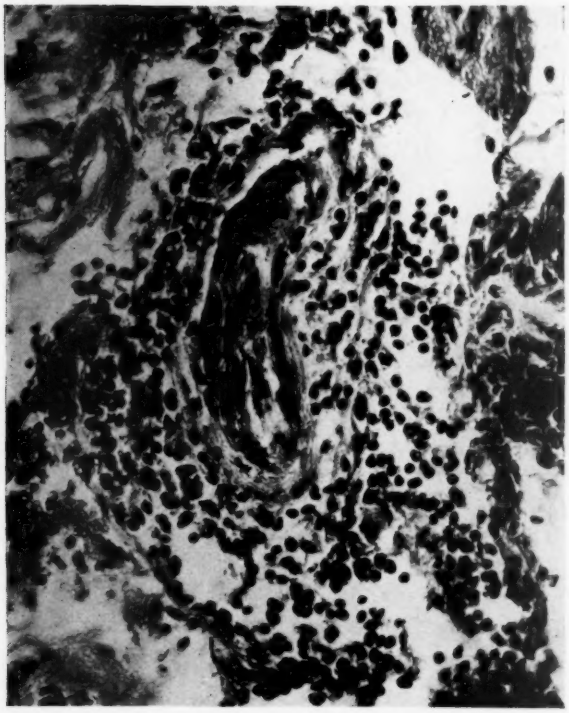

Fig. 11.—Case 8, oesophagus. Recent necrosis of large arteriole with round cell response. Haematoxylin and eosin. × 250.

Fig. 12.—Case 17, right breast. Segmental necrosis and subacute arteritis. Haematoxylin and eosin. × 100.

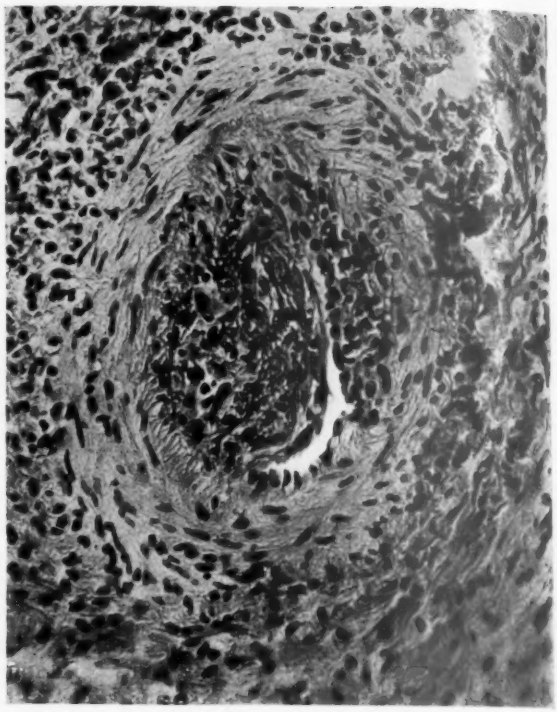

Fig. 13.—Case 4, subcutaneous nodule. Small artery in outer zone with intimal and adventitial infiltration. Haematoxylin and eosin. × 200.

Fig. 14.—Subcutaneous nodule obtained at biopsy in a case of juvenile rheumatoid arthritis. Haematoxylin and eosin. × 100.

although sections were examined from lung, liver, kidney, and spleen in all cases, and from other tissues such as gut, pancreas, lymph nodes, pituitary, adrenal, brain, and bone marrow in up to one-third of the total series.

Discussion

Arteritis, or evidence of previous arteritis, was found in eighteen of the 72 cases of rheumatoid arthritis studied at autopsy. These eighteen cases have been subdivided into two groups on the basis of the presence or absence of cardiac lesions indicative of rheumatic carditis. Practically all the arterial changes seen in Group I can be identified with past or present rheumatic carditis, and with one exception they were confined to the heart. In Group II there was no evidence of rheumatic heart disease, nor were any of the other conditions present which are associated with more or less generalized arteritis, *e.g.* polyarteritis nodosa, systemic lupus erythematosus, etc. The other pathological processes found at autopsy in this group are listed in Table IV. It is thus evident that the only features common to this group of eleven cases are rheumatoid arthritis and arteritis.

TABLE IV

ASSOCIATED DISEASES IN ARTERITIS IN RHEUMATOID ARTHRITIS CASES WITHOUT RHEUMATIC HEART DISEASE

Case No.	Disease
1	nil
2	pyelitis, early amyloidosis
3	post-hepatitic cirrhosis, carcinoids
5	transverse "myelitis", hypertension
6	nil
8	acute liver necrosis, recent mild gold dermatitis
9	bilateral thalamic infarcts
12	fractured femur, cystitis
13	pulmonary tuberculosis
14	nil
17	bronchial carcinoma

The changes seen in the vessels were very similar to those described in the muscles by Sokoloff and others (1951). The vessels involved were usually small arteries of the muscular type, though arterioles can be affected (Cases 2 and 5). The anatomical distribution favoured those tissues in which other lesions are known to occur in rheumatoid arthritis—the heart (nine cases), peripheral nerves (five cases), skeletal muscles (three cases), and synovial tissue (one case). Arteritis was only occasionally seen in the viscera, and did not occur in the organs usually affected in other forms of arteritis. Damage to the vessel was usually less severe than that encountered in polyarteritis nodosa, so that aneurysm formation was not seen and thrombosis was seen only twice (Cases 8 and 11). Nevertheless, necrosis was a feature in a few instances (Cases 2, 8, and 17), and destruction of elastic tissue and haemosiderin pigment were also encountered. The cellular reaction was of subacute type and affected the adventitia to a greater extent than the other two coats. That the vascular damage may occur over a considerable period of time is indicated by the presence of lesions at several stages of development in some of the patients (Cases 5, 8, 13, and 17).

None of these arterial lesions is specific, but the changes encountered in these cases of rheumatoid arthritis differ in several respects from the lesions of other types of arteritis. Viscera other than the heart have been examined in a sufficient number of cases of rheumatoid arthritis to indicate that they are not usually involved. The anatomical distribution, apart from the heart, differs from that of rheumatic fever, polyarteritis nodosa, systemic lupus erythematosus, dermatomyositis, scleroderma, Henoch-Schönlein purpura, or temporal arteritis. The last two conditions can also be distinguished by the morphology of the lesions. Although individual lesions encountered in rheumatoid arthritis and in the other arterial diseases have certain resemblances, the rheumatoid cases lack the other changes characteristic of these diseases, and the general picture of the vascular changes in rheumatoid arthritis differs from that in the other diseases.

The high incidence of cardiac arteritis in rheumatoid arthritis helps to explain some of the difficulties in the interpretation of the cardiac pathology of the disease. The occurrence of rheumatic heart disease in various studies has been reviewed recently by Sokoloff (1953), who records an incidence varying from 18 to 66 per cent. These figures cannot be regarded as completely accurate, for most of the studies have been reported from America and include cases of ankylosing spondylitis along with those of rheumatoid arthritis. However, when allowance is made for such cases the figures still show a similar wide divergence. This may be partly due to sampling errors, for several of the series have been small, but a more important factor is the variation in the criteria of diagnosis of the cardiac lesions. In the present series, only severe valvular damage (other than calcific aortic stenosis), active valvulitis, myocardial Aschoff bodies, and involvement of the left endocardium were accepted as diagnostic of rheumatic heart disease, and by

these criteria, twelve cases (17 per cent.) were found to be affected. Very similar criteria were adopted by Bayles (1943) and Bennett (1943), who recorded incidences of 23 and 15 per cent. respectively in smaller series; in Sokoloff's series of 105 cases, 4 per cent. showed "frank rheumatic heart disease". Most writers who have recorded higher incidences do not define their criteria of rheumatic heart disease with precision, and some even include cases with only pericarditis (Young and Schwedel, 1944). If cases showing such features as pericarditis, arteritis, perivascular scars, and diffuse myocarditis in some combination were included in this series, the incidence would correspond to the higher figures previously reported, for by these standards forty cases (55 per cent.) could be regarded as positive. Coronary arteritis of the type seen in polyarteritis nodosa has been recorded by many observers in rheumatic carditis (Geipel, 1907; Wohlwill, 1923; MacCallum, 1925; Klinge and Vaubel, 1931; Wild, 1933; Collins, 1938; Rich and Gregory, 1943; McKeown, 1945; de Brux, 1948; Pagel, 1951), and vascular lesions of the same type have been described in systemic lupus erythematosus (Klemperer and others, 1941; Coburn and Moore, 1943; Griffith and Vural, 1951), in dermatomyositis (Fahr, 1921), and in scleroderma (Pollack, 1940). Many of the arterial lesions described in the heart in rheumatoid arthritis in this and previous studies have represented the end result of an active arteritis. It is probably justifiable to regard such old lesions as rheumatic if other diagnostic lesions are present (Group I), but such a conclusion does not seem warranted in the absence of other evidence of rheumatic heart disease (Group II). Likewise pericarditis as an isolated finding cannot be regarded as rheumatic (Smith and Willius, 1932), and diffuse or focal myocarditis without Aschoff bodies occurs in many conditions other than rheumatic carditis (Saphir, 1941, 1942).

Although this study indicates that arteritis is an important feature of the pathology of rheumatoid arthritis, it affords no clue to the pathogenesis of the arteritis. Analysis of the cases in Group II shows no striking correlation between the arteritis and any other feature of the disease. The average age of the patients and the sex incidence are the same as that for the whole series of 72 cases. Clinical activity at the time of death was seen in a much higher proportion of cases in Group II (6/11) than in the remaining cases where such information was available (14/58). But an attempt to connect arteritis in the heart, synovial tissue, muscles, and nerves with other lesions in these situations does not provide any outstanding correlation. Thus, the single example of an arterial lesion in synovial tissue occurred in the absence of active inflammation, whereas the examination of multiple blocks obtained either at biopsy or autopsy from over sixty cases, though frequently showing active synovitis revealed no other instance of arteritis. In muscles and nerves, lymphorrhages and arteritis occurred independently of one another, and even when both were present the two lesions were usually unrelated. The arterial lesions in the oesophagus of Case 8 and in the pancreas and periosteum of Case 17 were not associated with any other lesion. The tracheal lesion in Case 2 lay within a large patch of fibrosis. The acute arteritis in the breast in Case 17 lay next to a focus of cystic hyperplasia and may have been aetiologically connected with this rather than with the arthritis; but acute necrotizing arteritis is a most unusual accompaniment of cystic hyperplasia. Although no adequate explanation was found for the thalamic infarcts in Case 9, there was no evidence of arteritis in the sections of brain studied. None of the nodules studied was sufficiently recent to provide data to support or refute the premise of Sokoloff and others (1953) that arteritis is a feature of the early stage of the rheumatoid nodule, or the earlier suggestion of Bennett and others (1940) that the central necrosis might be due to infarction. Such lesions as were seen in nodules could readily be interpreted as secondary rather than primary.

No association could be established between the arteritis and any therapeutic agent, except possibly in Case 8. This patient had a mild gold dermatitis 3 weeks before his death. The skin lesion cleared up within a few days on BAL treatment, and no other evidence of a reaction to gold was seen clinically or in the tissues. Death was due to acute liver necrosis accompanying viral hepatitis. Gold was used in treatment in many other cases in the whole series, including Cases 1 and 2, but no lesions attributable to toxicity were seen. Toxic reactions in eight cases lacking evidence of arteritis were directly related to the fatal outcome. The writer is not aware of any record of arteritis complicating treatment with gold in human patients, nor accompanying the production of renal damage with large doses in animals (Brown and others, 1926; Orestano, 1933; Cortell and Richards, 1942). None of the patients in this series had received ACTH or cortisone.

The incidence of arteritis in rheumatoid arthritis is probably considerably higher than that recorded here, for several cases were incompletely examined. Excluding the twelve cases with rheumatic heart disease, multiple blocks were taken from the heart in 33 cases, eight of which showed arteritis, whereas

a single block was taken in 27 cases and only one showed arteritis. Synovial tissue, muscle, and nerve were examined in only one-third to one-half of the total number of cases. Examination of serial sections might also have increased the incidence.

Summary

(1) Vascular lesions were sought for in the heart and in other organs and tissues in 72 fatal cases of rheumatoid arthritis.

(2) Arteritis, past or present, was encountered in eighteen cases. In seven of these, lesions diagnostic of rheumatic heart disease were also found and the vascular involvement was mainly confined to the heart. In the remaining eleven cases, there were no pathological processes other than rheumatoid arthritis which might be associated with the arteritis, and the vascular lesions are considered to be the arteritis of rheumatoid arthritis.

(3) The arteritis of rheumatoid arthritis was encountered most frequently in the heart, muscles, and nerves, and occasionally in synovial tissue. No vascular lesions were encountered in those viscera which are commonly affected in other forms of generalized arteritis, though diseased vessels were sometimes found in certain unusual situations, *e.g.* periosteum, oesophagus, trachea.

(4) The arteritis usually seemed to be of subacute form, sometimes with necrosis, and it affected small arteries or arterioles. Thrombosis was unusual and aneurysm formation was not seen. Individual patients sometimes showed arterial lesions in different stages of development.

(5) The pathogenesis of the arteritis remains obscure. The vascular lesions were never regularly associated with any other lesion.

(6) The arteritis of rheumatoid arthritis, though not specifically identifiable, can be differentiated from that of polyarteritis nodosa, rheumatic fever, systemic lupus erythematosus, temporal arteritis, dermatomyositis, and scleroderma.

(7) The relation of arteritis of coronary vessels to the incidence of rheumatic heart disease in rheumatoid arthritis is discussed.

(8) The incidence of arteritis in rheumatoid arthritis is probably considerably higher than that recorded in this study.

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L'artérite de l'arthrite rhumatismale

RÉSUMÉ

(1) On a recherché les lésions vasculaires dans le coeur et dans les autres organes et tissus des 72 cas mortels d'arthrite rhumatismale.

(2) On a trouvé de l'artérite, récente ou ancienne, dans 18 cas. Dans sept d'entre eux on a aussi trouvé des lésions diagnostiques de la maladie rhumatismale du coeur dont l'atteinte vasculaire était presque exclusive. Dans les onze cas restants on n'a pas trouvé de processus morbide autre que l'arthrite rhumatismale; on peut donc considérer ces lésions vasculaires comme représentant l'artérite de l'arthrite rhumatismale.

(3) On a trouvé l'artérite de l'arthrite rhumatismale le plus souvent dans le coeur, les muscles, les nerfs et quelquefois dans le tissu synovial. On n'a pas trouvé de lésions vasculaires dans les viscères habituellement atteints dans d'autres formes d'artérite généralisée, bien qu'on ait rencontré des vaisseaux malades aux endroits inaccoutumés, tels que périoste, oesophage ou trachée.

(4) L'artérite apparaissait généralement sous sa forme subaiguë, quelquefois avec nécrose, l'atteinte portant sur les petites artères et les artérioles. La thrombose était rare et il n'y avait pas de tendance à l'anévrisme. Certains cas présentaient des lésions artérielles aux différents étapes évolutifs.

(5) La pathogénie de l'artérite demeure obscure. On n'a jamais observé d'association constante entre la lésion vasculaire et une autre lésion définie.

(6) L'artérite de l'arthrite rhumatismale, bien que sans identité spécifique, peut être différenciée de celle de la polyartérite noueuse, du rhumatisme articulaire aigu, du lupus érythémateux disséminé, de la dermatomyosite et de la sclérodermie.

(7) On discute le rapport entre l'artérite des vaisseaux coronaires et la fréquence de la maladie rhumatismale du coeur au cours de l'arthrite rhumatismale.

(8) L'artérite de l'arthrite rhumatismale est probablement bien plus fréquente qu'il ne ressort de cette étude.

Arteritis de la artritis reumatoide

SUMARIO

(1) Investigáronse lesiones vasculares del corazón y de los demás órganos y tejidos en 72 casos mortales de artritis reumatoide.

(2) Se encontró una arteritis, reciente o antigua, en 18 casos. En siete de éstos encontráronse también lesiones diagnósticas de la enfermedad reumática del corazón; la afección vascular de éste fué casi exclusiva. En los demás once casos la artritis reumatoide fué el único proceso mórbido encontrado y las lesiones vasculares se puden, pués, considerar como arteritis de la artritis reumatoide.

(3) La arteritis de la artritis reumatoide encontrose más frecuentemente en el corazón, en los músculos, los nervios y, a veces, en el tejido sinovial. No se encontraron lesiones vasculares en vísceras generalmente afectadas en otras formas de arteritis generalizada, aunque se hubiese encontrado vasos enfermos en sitios poco comunes, como en el perióstio, el esófago o en la tráquea.

(4) La arteritis presentábase generalmente en forma subaguda, a veces con necrosis y afectaba las pequeñas arterias y arteriolas. Trombosis fué rara y formación de aneurismo no se vió. En casos individuales se vió a veces lesiones arteriales en varias etapas evolutivas.

(5) La patogénesis de la arteritis queda oscura. No se observó asociación constante entre la lesión vascular y alguna otra lesión.

(6) La arteritis de la artritis reumatoide, aunque sin identidad específica, se puede diferenciar de la de la poliarteritis nodosa, del reumatismo poliarticular agudo, del lupus eritematoso diseminado, de la dermatomiositis y de la esclerodermia.

(7) Se discute la relación entre la arteritis de los vasos coronarios y la frecuencia de la enfermedad reumática del corazón en el curso de la artritis reumatoide.

(8) La arteritis de la artritis reumatoide es probablemente mucho más frecuente de lo registrado aquí.

OSTEITIS CONDENSANS ILII AND ITS DIFFERENTIATION FROM ANKYLOSING SPONDYLITIS

BY

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Sicard, Gally, and Haguenau (1926) first described cases of the condition now known as osteitis condensans ilii. The name of the disease was introduced by Bársony and Polgár (1928), who recorded fifteen cases; they considered it to be a specific clinical entity, the lesion being found on radiological examination of the lumbo-sacral area, and the essential feature being dense sclerosis in the iliac bone, adjacent to the lower part of the sacro-iliac joint.

Review of the Literature

Bársony and Polgár (1928) described fifteen cases which they saw within 18 months, an indication that the disease is not rare. All their cases complained of low back pain, and tenderness was noted over the sacro-iliac joints. The lesions could be unilateral or bilateral, and the site of pain coincided with the *x*-ray lesion in unilateral cases. In cases with bilateral involvement the pain was felt diffusely in the lower lumbar region. Some patients also had neuralgic pains in the lower limbs. The disease ran a chronic course, and, although relieved by heat and exercises, tended to relapse. Bársony and Polgár stated that "limited changes" occurred in the joint spaces in some of their cases, and that follow-up *x*-rays were needed to distinguish osteitis condensans ilii from "sacro-iliac arthritis". They offered no firm opinion regarding the aetiology of the condition, but suggested that there might be some disease of the sacro-iliac joint, or that some mechanical strain of the sacro-iliac joints could account for the site of the sclerosis. In a subsequent paper, Polgár (1933) drew attention to the fact that Paget's disease of the ilium could commence in that area of the bone affected by osteitis condensans ilii and simulate the latter condition.

Berent (1933, 1934) described three cases in female patients. He stated that the condition only occurred in women, and that it resulted from damage to the sacro-iliac joints during pregnancy and confinement. The ligaments were relaxed during pregnancy and allowed more movement of the joints. As a result, the ligaments might be stretched or torn, with accompanying periosteal damage.

Pines (1932) described two cases, one of which was a male. Both cases had unilateral disease, and joint tenderness coincided with the site of the lesion.

Rendich and Shapiro (1936) reported twelve cases, three of them in males. While some of their patients had low back pain, sciatica, and tenderness over one or both sacro-iliac joints, others had no symptoms referable to the affected area. These authors cast doubt upon the condition as a cause of low back pain. They stated that the joint outline was normal, and stressed the importance of taking oblique radiographs so as to demonstrate clearly the sacro-iliac joint.

Shafar (1938) reported a case in a male. He stated that the joint spaces were normal in this patient.

Hare and Haggart (1945) recorded their findings in 23 cases. Subsequently, Shipp and Haggart (1950) augmented this account, and reported a total of one hundred cases seen at the Lahey clinic over a period of 13 years. They reviewed all cases seen up to 1946, and, in 29 cases, amended the diagnosis from osteitis condensans ilii to ankylosing spondylitis. All patients in this large series were women; 78 had borne children, and 48 of them dated their symptoms from their pregnancy. The authors considered the sacrum and the sacro-iliac joints to be normal. They advanced the theory that in the female the sacro-iliac joint lies in the sagittal rather than the normal oblique plane, and in pregnancy further strain is put on the articular surfaces owing to relaxation and stretching of the pelvic ligaments. Obesity was a factor in 64 cases. Tests involving movements of the joints did not provoke pain.

Szabados (1947) reported five cases, in three of which there was evidence of a chronic urinary infection; in another two cases a history of pyelitis was obtained. It was considered that the renal and ureteric infection could spread to the nutrient foramina in the iliac bone.

Ude (1950) described six cases in which he also found residual changes of Scheuermann's disease. He suggested that the iliac changes were either secondary sclerosing changes superimposed on an old sacro-iliac epiphysitis, or that the sacro-iliac changes were secondary to the directional strain placed on these joints by variations in the curvature of the spine. In three cases there was an associated degenerative process in the region of

the pelvic symphysis. Subsequently, Ude (1952) reported more than thirty similar cases.

Knutsson (1950) presented the radiological findings in 147 cases of ankylosing spondylitis and in 37 cases of osteitis condensans ilii. In 32 of the patients with condensans ilii, the joint spaces appeared to be normal, and the articular surfaces were unchanged. While indicating that in the early stages of spondylitis it might be difficult to differentiate the changes from those of osteitis condensans, Knutsson felt that such a differentiation could be made at a later stage.

Baker and others (1950), on the other hand, considered that the two conditions were related, and he included six cases of condensans ilii in a series of one hundred cases of ankylosing spondylitis, treated by roentgen therapy. He felt that the conditions were identical because of their identical anatomical situation, clinical symptoms and response to treatment.

Layani and others (1950) reported a single case in a male patient, in whom there was a complicating factor of severe trauma with injury to a hip joint. They obtained a portion of affected bone and examination showed an overgrowth of bone, a periosteal osteophytosis and fibrous periosteal reaction.

Gillespie and Lloyd-Roberts (1953) described 21 cases, all occurring in females who had borne children. They did not consider that the back pain was due to the sacro-iliac lesions, or that the physical findings were related to the radiological appearances. While stressing the incidence of sacral changes, they felt that the probable explanation was an obliterative endarteritis. These authors considered that there was evidence of a prolapsed lumbar disk in thirteen of their cases, and they felt that this was responsible for the pain; in the remaining eight cases the pain was considered to be due to other causes, not elicited.

Hutton (1953) has recently described a series of 28 cases, which included two men. He stated that in 22 cases there was a history of back pain, and in six the condition was discovered accidentally during pyelographic or other radiological examination.

Pathological Changes.—Rendich and Shapiro (1936) obtained a biopsy specimen from one patient who, because of persistent pain, had a sacro-iliac fusion performed. Dr. W. Hala reported on this section as showing marked condensation of the osseous tissue with obliteration of the lacunae. No osteoblasts or osteoclasts were seen. The marrow spaces contained an unusual number of myocytic and plasma cells. There were occasional depositions of lime salts in the condensed bone, occurring more or less parallel to the lamellae of the bone.

Hare and Haggart (1945) studied the findings in two cases from whom biopsy specimens were obtained. The bony trabeculations were greatly increased in density, but the lacunae were still discernible. Scattered islands of cartilage were noted at a considerable distance from the joint surface. The bone marrow showed focal areas of fibrosis. There was osteoblastic activity in excess of the normal in the form of clumps of osteoblasts and occasional osteoclasts. Macroscopically the articular cartilage was fibrillated and irregular.

Gillespie and Lloyd-Roberts (1953) obtained a biopsy specimen from a patient with marked bilateral condensans ilii, in whom the sacro-iliac joints appeared radiologically to be normal. Prof. S. L. Baker reported that the articular cartilage and ligaments were normal, and the main findings in the bone were of concentric osseous deposits, thickened lamellae and narrow Haversian canals.

Radiological Appearances.—These have been described in detail by several authors, notably Bársony and Polgár (1928), Knutsson (1950), and Gillespie and Lloyd-Roberts (1953). There is a disturbance of the normal architecture of that part of the iliac bone which lies in proximity to the sacro-iliac joint. The characteristic lesion is a uniform area of dense sclerosis, approximately triangular or aliform in shape, the base of which lies on the iliac border of the sacro-iliac joint. The apex of the lesion spreads into the auricular portion of the ilium to a variable degree. The smallest lesion merely occupies the angle at the lower end of the sacro-iliac joint, but sometimes a large lesion is seen extending through the ilium towards the pubic ramus, the base of the lesion occupying the entire iliac border of the sacro-iliac joint. The condition is bilateral in the majority of cases.

The outer margin of the sclerosis often presents a well-defined edge if the film has been over-exposed. Close examination shows, however, that there is a gradual transition from the dense opacity of the lesion to the zone of completely normal bone. In some cases the lateral margin of the lesion is grossly irregular.

Although the sclerosis appears to be very dense and of uniform consistency, it has been noted that the cancellous structure of the bone has been preserved. This is more evident if the film has been slightly over-exposed.

Sclerotic changes are seen in the sacrum in a small proportion of cases. Since Bársony and Polgár first reported this feature, several other workers have commented upon its occurrence, especially Rendich and Shapiro (1946) and Gillespie and Roberts (1953). Because of the oblique position of the sacro-iliac joint, it is impossible to say on the study of the antero-posterior film alone whether the sacrum and sacro-iliac joint are affected. Oblique views of the sacro-iliac joints and tomographs will establish the true location of the changes. Tomography has been used to prove that the lesion extends to a depth of several centimetres into the bony substance.

Thus far all authorities are agreed, but there is a considerable amount of controversy regarding the question of alterations in the margins of the sacro-iliac joint. Bársony and Polgár (1928) reported limited changes in the sacro-iliac joints in some of their cases, and that serial *x* rays were required to distinguish osteitis condensans ilii from "sacro-iliac arthritis". These authors were probably referring to the sacro-iliitis seen in ankylosing spondylitis, as the significance of this finding was not fully appreciated until Scott (1942) stressed the initial involvement of the sacro-iliacs in spondylitis. Pines

(1932) considered that his second patient, a female, might have a sacro-iliitis. Ude (1950) mentioned that in one of his cases, that of a female patient with unilateral disease, there was narrowing of the sacro-iliac joint adjacent to the affected bone. Knutsson (1950) reported narrowed joint spaces and lip shaped protrusions from the edges of the articular margins in some of his cases, and stated that, although the distinction between osteitis condensans ilii and ankylosing spondylitis was easy in the majority of cases, there were border-line cases, with insignificantly developed sclerosis on the iliac margin and seemingly intact joint spaces, in which initially it was impossible to make a differential diagnosis.

Rendich and Shapiro (1936), Hare and Haggart (1945), and Gillespie and Roberts (1935) all maintained that the sacro-iliac joints are not affected in osteitis condensans ilii. All these authors studied the sacro-iliac joints by oblique radiographs and tomograms.

Other radiological findings reported in cases of osteitis condensans ilii have been

(*a*) changes in the pubic symphysis with sclerosis and small cystic spaces (Ude, 1950; Gillespie and Roberts, 1953);
(*b*) Garre's sclerosing osteitis (Szabados, 1947);
(*c*) evidence of old spinal osteochondritis (Ude, 1950);
(*d*) bony islets in other regions of the skeleton, reported in occasional cases.

Present Study

Material.—In view of the many divergent opinions regarding osteitis condensans ilii, especially with regard to its significance, clinical features, aetiology, and radiological appearances, a further series of twenty cases is here presented. All twenty cases had an initial *x* ray which suggested the diagnosis of osteitis condensans ilii. The patients have been investigated since July, 1950. In each case a full clinical, radiological, and haematological investigation was performed; the serum calcium, phosphorus, and alkaline phosphatase were measured; the Wassermann reaction was tested. An intravenous pyelogram was performed in five cases in which there was a history indicative of a previous urinary infection. Five of the patients were admitted to hospital, and the remainder were investigated at the Out-patient Department.

Results

Symptoms.—All the patients in the series were females, and all had a complaint of low back pain. Their ages ranged from 26 to 47 years (mean 35·1). The duration of symptoms ranged from 2 to 14 years (mean 7·05). The age at onset varied from 18 to 41 years (average 28).

The onset of the pain occurred during pregnancy or in the puerperium in eleven cases. Two patients had had children since the onset of their symptoms without any increase in symptoms or any relapse. Three patients stated that successive pregnancies increased the pain. Five of the patients were nulliparous.

The back pain was felt in the lumbo-sacral area, usually most marked just to one or other side of the midline. In eighteen of the cases (90 per cent.) pain radiated to one or other hip, or beyond. In nine cases there was bilateral sciatic radiation.

The pain was usually described as dull, persistent, and "nagging" in character. Sudden movements, and any physical activity involving the lumbo-sacral area, aggravated the pain. Coughing, sneezing, and straining at micturition or at stool, did not usually cause increased discomfort. With only one exception, the patients remarked that the pain was aggravated at the time of the menstrual periods, and in several cases the symptoms had been originally attributed to dysmenorrhoea.

All the patients experienced periods of complete or partial remission, which varied from a few weeks to 3 years; the attacks of pain lasted from 2 weeks up to 5 months, and five patients stated that they were never completely free from some discomfort. Three patients gave a definite history of a flexion injury in the back, consistent with a prolapsed lumbar intervertebral disk lesion. In only two patients was any history given of a near relative affected by low back pain. *X* rays of these relatives did not reveal any abnormality in the sacro-iliac region.

Eleven patients complained of marked stiffness of the spine in the mornings; this stiffness gradually wore off as the day progressed.

Physical Features.—The principal physical findings on examination of the spine are shown in Table I. No constant associated abnormalities or physical defects were noted, the principal complicating dis-

TABLE I

PRINCIPAL PHYSICAL FINDINGS ON SPINAL EXAMINATION OF TWENTY CASES OF "OSTEITIS CONDENSANS ILII"

Physical Sign		No. of Cases
Tenderness over Sacro-Iliac Joints		17
Spinal Deformity		4
Restricted Spinal Movements	all movements: 5	13
	extension and flexion: 3	
	flexion: 1	
	extension: 4	
Positive Straight-Leg Test		2
Pain on Movement of Sacro-Iliac Joints		16
Obesity		5

TABLE II

RADIOLOGICAL CHANGES IN TWENTY FEMALES INITIALLY DIAGNOSED AS CASES OF OSTEITIS CONDENSANS ILII

Case No.	Age (yrs)	Sacrum Involved	Sacro-Iliac Joint	Spine	Other Changes
1	40	0	Spaces normal Lipping at lower margin, right side	Slight sclerosis L5 region	Opaque maxillary sinuses
2	36	+	Narrowed space Lipping of right joint	Mild osteo-arthritic changes ? osteochondritis	Slight irregularity of manubrio-sternal joint
3	34	0	Normal	Minor osteo-arthritis of thoracic spine Narrow L4/5 space	—
4	47	0	A little lipping at lower margins	Minor osteo-arthritis of C5/6	Cystic changes in pubis
5	34	0	Normal	Schmorl's node in T7	—
6	40	+	Lipping at lower margin of right joint	—	—
7	36	0	Narrowing of lower part of joint spaces	—	—
8	43	0	Lipping at lower margin	Mild osteo-arthritis in thoracic and LV5 regions	Slight irregularity in manubrio-sternal joint surfaces
9	31	0	Normal	—	—
10	35	0	Normal	Schmorl's node in LV3	—
11	30	+	Narrowing of joint spaces in inferior parts	Narrowed LV5/S1 joint space	—
12	26	+	Narrowing of joint spaces with minor irregularity	Mild changes of osteochondritis in thoracic spine	Healed T.B. focus in lung
13	44	0	Lipping at lower margin	Gross kypho-scoliosis	Left renal calculus
14	30	0	Minor sclerosis and erosion Sub-marginal osteoporosis	—	Iritis Erythrocyte sedimentation rate raised Increasing limitation of spinal movements
15	30	0	Minor erosions along iliac border of right joint	—	Slight erosion of manubrio-sternal joint Erythrocyte sedimentation rate raised
16	35	+	Irregular widening, erosion, and osteoporosis	Failure of fusion of a few epiphyses	—
17	30	+	Marginal erosions	? involvement of apophyseal joints	Cystic changes in pubis Manubrio-sternal joint ankylosed Erythrocyte sedimentation rate raised
18	33	0	Irregular joint space right side	? squaring of lumbar vertebrae	—
19	27	+	Patchy erosions and widening	—	Increasing limitation of spinal movements Erythrocyte sedimentation rate raised
20	42	+	Irregular widening and erosions	? squaring of lumbar vertebrae	Mitral cardiac lesion Calcaneal spurs

Cases 1-13: Osteitis condensans ilii (mean age 36·6 yrs)
Cases 14-20: Ankylosing spondylitis (mean age 32·4 yrs)

orders being mild obesity (five cases), and maxillary sinusitis, mitral stenosis, healed pulmonary tuberculous focus (one case), cervicitis and iritis (one case), and renal calculus and pyelonephritis (one case).

Radiological Examination.—The radiological changes in the present series are shown in Table II. They are recorded in detail because of the conflicting descriptions that have been given by various authorities in the past. The illustrations also

provide evidence of the range of changes that may be seen (Figs 1-8).

The condition was bilateral in all but two cases, and the lesions varied considerably in size (Figs 1 and 2). The margin of the lesion was usually fairly distinct and even, but occasionally irregular. The sacrum was involved in seven cases, a feature that was demonstrated by means of an oblique radiograph of the sacro-iliac joints (Fig. 4).

Detailed study of the radiological features elicited some points of interest. All the cases in this series were initially considered to be cases of osteitis condensans ilii, inasmuch as the posterior-anterior radiograph of the pelvis showed dense sclerosis in the lower iliac region of the sacro-iliac joint, with an apparently normal joint outline. In seven cases, however, oblique views of the sacro-iliac joints showed minimal but definite abnormalities of the joint margins in the inferior cartilaginous region of the joint (Cases 14-20, Table II). These changes consisted in erosions of the joint margin with patchy areas of submarginal osteoporosis, and some resulting patchy, irregular widening of the joint space (Fig. 8). They were interpreted as indicating

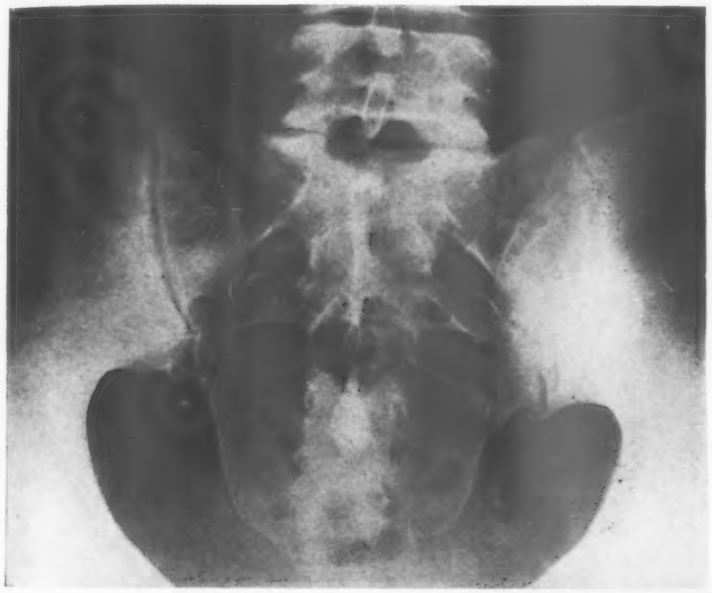

Fig. 1.—Case 2, female aged 33 years, osteitis condensans ilii, lesion restricted to left ilium.

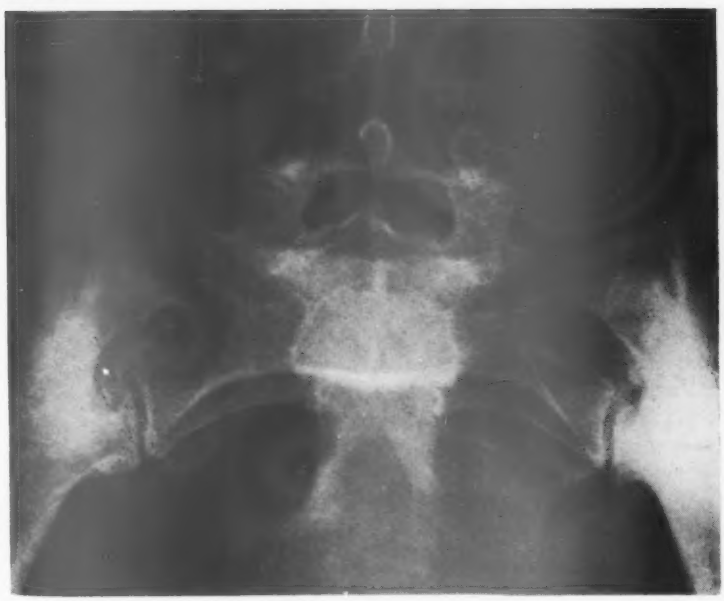

Fig. 2.—Case 5, female aged 32 years, osteitis condensans ilii, marked bilateral lesions.

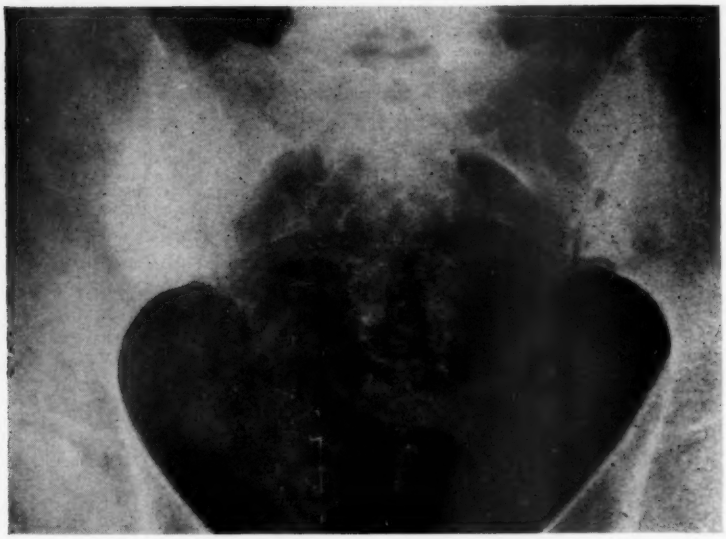

Fig. 3.—Case 3, female aged 36 years, bilateral osteitis condensans ilii, with predominant changes in right ilium.

destruction of the cartilage, an osteoclastic process. These seven patients were considered to be cases of ankylosing spondylitis.

Further consideration and study of the clinical course of these seven cases has lent support to this view. Thus, in four cases, the erythrocyte sedimentation rate has intermittently become raised. One patient developed iritis, one had calcaneal spurs, and two patients developed progressive limitation of spinal movements compatible with ankylosing spondylitis. All these seven patients have had rest, physiotherapy, and the usual conservative treatment for low back pain—without any relief. Four have since had radiotherapy with benefit; the other three patients have deferred treatment. These seven patients all had a complaint of marked morning stiffness, and all had bilateral lesions. In no instance in this group was there any other lesion present which could be held to account for the low back pain.

In the remaining thirteen cases, classed as osteitis condensans ilii, there are four cases in which the differentiation from ankylosing spondylitis has proved difficult. However, in these thirteen cases, the sacro-iliac joint spaces have shown no abnormality, apart from slight narrowing, minimal irregularity or lipping. In the osteitis condensans ilii group, the symptoms have been milder, periods of prolonged remission commoner, and response to conservative methods of treatment better, than in the spondylitis group. The erythrocyte sedimentation rate has remained within normal limits, there have been no signs of any systemic disturbance, and no progression in the limitation of joint movement. Morning stiffness was not a marked feature in the patients with osteitis condensans ilii, except in those patients who had concurrent osteoarthritic changes. The principal differences between the groups are shown in Table III (opposite).

The *x*-ray changes were unilateral in two cases (Fig. 1), and predominantly unilateral in four other cases (Fig. 4). There was a correlation between the site of the lesion (as shown on *x* ray), the site of the pain, and the localization of the sacro-iliac tenderness and pain. In no instance did the patient localize the pain over a normal joint. In two cases the principal symptoms were referred to the less grossly affected ilium (as judged radiologically). In several cases a grossly involved region was not tender or painful on movement.

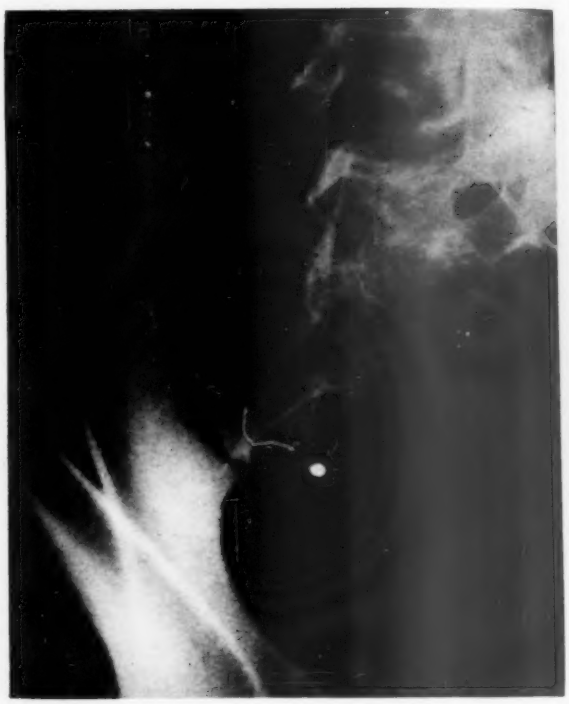

Fig. 4.—Case 3, oblique radiograph of right sacro-iliac joint, showing narrowed joint space in inferior region. Marked sclerosis is seen in the iliac bone, and a little sclerosis involving the sacrum.

X rays of the remainder of the spinal column and long bones did not reveal any constant abnormality. The findings are listed in Table II.

Differential Diagnosis.—The differentiation

TABLE III

COMPARISON BETWEEN FEATURES OF OSTEITIS CONDENSANS ILII AND EARLY CASES OF ANKYLOSING SPONDYLITIS

Diagnosis	Ankylosing spondylitis	Osteitis condensans ilii
Sex Incidence	Predominantly male	Predominantly female
Relation to Pregnancy	Not usual	Very common
Symptoms	Stiffness and pain	Pain more than stiffness
Signs	Some restriction of spinal movement often present	Restriction of spinal movements not a marked feature
Lesions	Bilateral	May be unilateral
X-ray Appearances	Patchy sclerosis with osteoporosis, and irregular widening of joint spaces	Sclerotic lesion, mainly in iliac bone, with relatively normal joint spaces
Systemic Disturbance (*e.g.*, loss of weight, anaemia, raised erythrocyte sedimentation rate)	May be present	Absent
Complications (*e.g.*, iritis, calcaneal spurs)	May be present	Absent

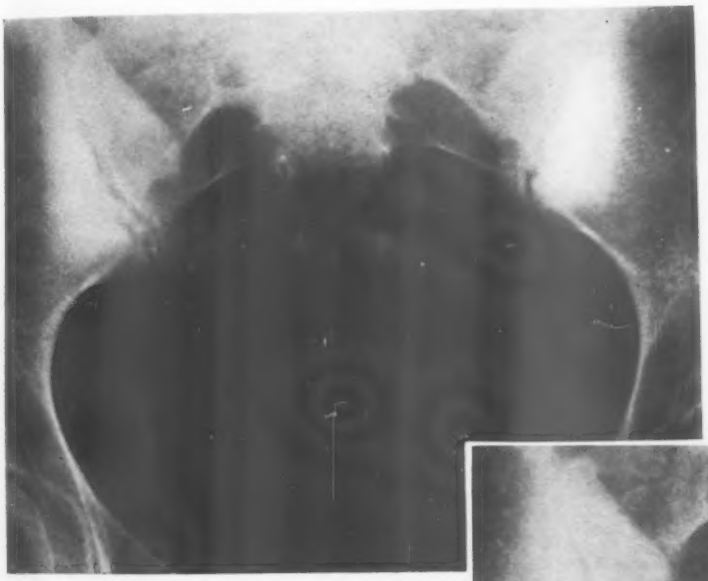

Fig. 5.—Case 14, female aged 31 years, radiograph taken in 1945 considered to be osteitis condensans ilii.

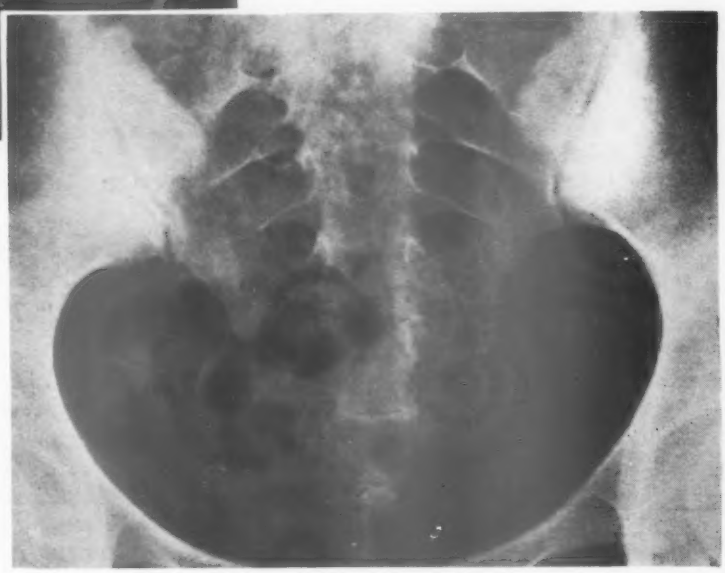

Fig. 6.—Case 14, radiograph taken in 1951, showing no substantial change from that taken 6 years previously. Although initially considered to be suffering from osteitis condensans ilii, this patient developed iritis and an intermittently raised E.S.R. in 1952, indicating a diagnosis of ankylosing spondylitis.

between osteitis condensans ilii and ankylosing spondylitis is the major issue, and the points of differentiation have already been considered in detail. Other sacro-iliac lesions which might cause difficulty in diagnosis are tuberculosis, Paget's disease (osteitis deformans), osteo-arthritis, and osteoplastic secondary deposits. However, the clinical features of these diseases, and close attention to the radiological appearances, should suffice to identify them.

Prognosis.—Osteitis condensans ilii runs a chronic course, but remissions are common and the response to treatment is usually good. The lesion usually shows little or no change over a period of years, although Shipp and Haggart 1950) found evidence of regression in (everal of their cases. In the present

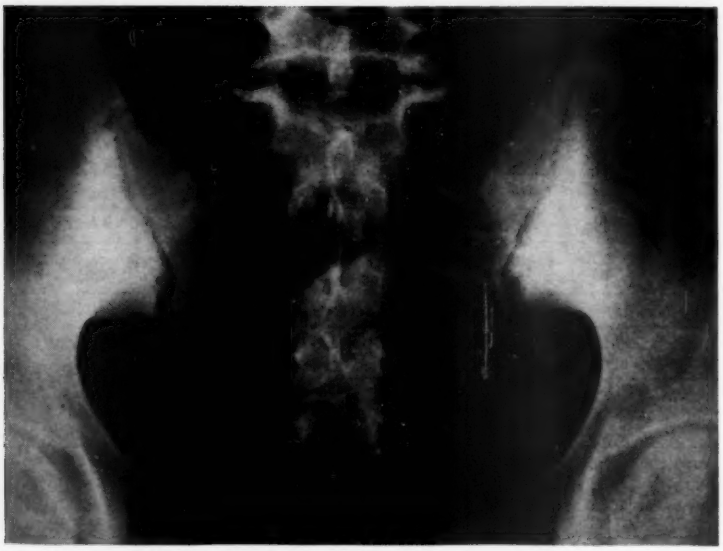

Fig. 7.—Case 19, female aged 27 years, with ankylosing spondylitis, radiograph of pelvis suggestive of osteitis condensans ilii. Sacro-iliac joints apparently normal.

Fig. 8.—Case 19, oblique radiograph of left sacro-iliac joint, showing submarginal osteoporosis, erosion of the iliac surface, and irregular widening of the joint space. Similar changes were found in the right sacro-iliac joint. Subsequent elevation of the E.S.R. and restricted spinal movements supported the diagnosis of ankylosing spondylitis.

series, no such evidence was obtained, although serial radiographs extending over 3 years were studied in most of the cases, and in two cases films were obtained dating back to 1945.

Treatment.—The majority of patients obtained substantial benefit from a simple conservative regime of treatment. This included:

(*a*) rest on a firm mattress;
(*b*) local application of heat by an electric pad or radiant heat lamp, and short-wave diathermy to the tender areas;
(*c*) spinal exercises to correct faulty posture;
(*d*) correction of obesity by dietetic measures when indicated;
(*e*) instruction in the avoidance of flexion strains to the spine, heavy lifting, and jarring movements;
(*f*) daily maintenance dose of analgesics adequate to control symptoms;
(*g*) spinal support to control symptoms (four patients).

Of thirteen patients, nine obtained substantial relief by the above regime, and one further patient had a remission in the early stages of treatment without any subsequent relapse. In one further case, complicated by gross congenital spinal deformity and renal calculus, it was not possible to give the full course of treatment or to assess the results. Only two patients failed to gain substantial benefit, but they have since improved and have had prolonged remissions.

Baker (1950) treated six cases by deep *x*-ray therapy to the sacro-iliac regions, and reported a good response. Although the risks of this therapy are slight (White, 1953), it is felt that it should be reserved for those cases that fail to respond to the conservative regime. In the present series, only one patient received deep *x*-ray therapy, and she relapsed after 6 months relief of symptoms.

Arthrodesis of the sacro-iliacs has been reported in a few cases (Rendich and Shapiro, 1936; Shipp and Haggart, 1950). Again, it is felt that this rather formidable surgical undertaking should be considered only for severe and intractable cases. It is difficult to understand how this operation should be successful in a condition in which the joint surfaces are virtually intact.

Discussion

Nomenclature.—The term osteitis condensans ilii has, by general usage, become accepted, although there is little to commend it. There is no clinical or pathological evidence of any inflammation, and the changes are not always restricted to the ilium. For these reasons the condition is often referred to as

"condensans ilii" or "osteitis condensans". At present the most suitable descriptive term would be sacro-iliac osteosclerosis, but until the pathogenesis of the condition is understood, the time-honoured designation of osteitis condensans ilii must suffice.

Aetiology.—The aetiology of osteitis condensans ilii is still unknown. The present series of cases lent no support to the theories that have involved trauma (Shafar, 1938; Layani and others, 1951); juvenile epiphysitis and a possible relationship to Scheuermann's disease (Ude, 1950, 1952); or chronic urinary infection (Szabados, 1947). No patient in the present series gave any history of trauma, and in only one case was infection of the urinary tract present. Minor changes, possibly indicative of mild vertebral epiphysitis, were seen in two cases, and Schmorl's nodes were noted in a further two patients (Table II). Many other investigators have failed to establish any relationship between osteitis condensans ilii and Scheuermann's disease.

The striking sex incidence of the disease and its common relationship to pregnancy (in nine cases out of thirteen in the present series), have led to several related theories concerning the aetiology and pathogenesis. Thus Berent (1934) considered strains during pregnancy and parturition led to ligamentous, capsular, and periosteal damage, but this theory has been invalidated by the finding, at operations, that the ligamentous and extra-articular structures were normal (Shipp and Haggart, 1950; Gillespie and Lloyd-Roberts, 1953).

Relaxation of the pelvic ligaments during pregnancy would allow more movements at the sacro-iliac joints, especially in view of the fact that the gynacoid pelvis is more obliquely set than the android, and the stabilizing ridges on the iliac joint surface are usually less prominent in women than in men (Shipp and Haggart, 1950). The absence of cartilaginous destruction and the comparative infrequency of sacral changes are factors which weaken this theory.

Another theory has invoked the pelvic obliterative endarteritis that follows parturition as a causative agent. An extension of this process to involve the nutrient artery supplying the affected region of the ilium could lead to ischaemic changes in the bone. Rendich and Shapiro (1936) have drawn attention to the constant position of a nutrient artery in the inferior juxta-articular region of the ilium, and this would account for the characteristic situation of the lesion. The grosser lesions would be accounted for by involvement of smaller vessels in the middle and superior regions of the joint. Support to this theory is given by the histological studies of affected bone (Rendich and Shapiro, 1936; Shipp and Haggart, 1950; Gillespie and Lloyd-Roberts, 1953). The histological appearances are those of a non-inflammatory calcium condensation, and are in keeping with an ischaemic process. Serious objections to the theory of pelvic endarteritis obliterans are the occurrence of cases in males and nulliparous females, and the absence of changes in other regions of the pelvis, *e.g.* the pubic articulations.

Ankylosing Spondylitis.—The clinical and radiological findings in the group of seven cases suggest that there is a restricted or abortive type of spondylitis which occurs especially in women. The symptoms are restricted to the lower lumbar area; the signs are minimal; the constitutional disturbance is negligible; the radiological evidence is predominantly that of sclerosis of the iliac bone adjacent to the sacro-iliac joint (Figs 5-8), with only slight evidence of the erosion and destruction seen in the more flagrant forms of the disease. The existence of this group accords with the experience of Tyson and others (1935) who stressed that spondylitis runs a milder course in women. Another investigator, White (1953), recently presented a series of one hundred cases of spondylitis in women, and stated that one-third had a normal erythrocyte sedimentation rate.

The existence of this group is of considerable interest, inasmuch as more widespread recognition of such cases would significantly alter the accepted sex ratio of the disease. Patients in this category should be offered deep *x*-ray therapy, as the disease may be more active. If they are not anxious to have therapy at this stage, they must be kept under periodic review.

It is possible that abortive or restricted cases are commoner than is thought, so that some of the credit claimed for radiotherapy in limiting the disease process, may be mainly due to the natural course of the disease.

Osteitis Condensans Ilii.—In the remaining thirteen cases, the diagnosis of osteitis condensans has been sustained. The lesions may be unilateral or bilateral, and there may be involvement of the sacrum. The joint spaces are usually normal; occasionally some slight narrowing and lipping at the lower margin may be seen, or some minimal irregularity. The patients have long remissions, and, although the onset may be related to a pregnancy, a subsequent pregnancy does not necessarily aggravate the symptoms. The erythrocyte sedimentation rate is within normal limits, there is no

associated systemic disturbance, and there are no consistent collateral findings on physical or radiological examination.

It is considered that osteitis condensans ilii is a specific clinical entity, occurring in women in over 90 per cent. of cases, often related to a pregnancy, and accompanied by low back pain. In no instance, in this series, could the condition be termed an incidental radiological finding. Although alternative causes for the back pain have been indicated by some authors, in only three patients out of the thirteen in this series was such an alternative explanation convincing.

Summary

A review of the condition known as osteitis condensans ilii is presented, and a further thirteen cases are described. It is considered that the condition is a specific pathological entity which can cause low back pain.

The differential diagnosis of osteitis condensans ilii is considered, with special reference to ankylosing spondylitis.

Seven cases initially diagnosed as osteitis condensans ilii, have now been recognized as examples of ankylosing spondylitis. These represent a restricted or abortive type of spondylitis, more common in women than in men.

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Ostéite condensante iliaque et sa differenciation de la spondylarthrite ankylosante

Résumé

On passe en revue l'affection connue sous le nom d'ostéite condensante iliaque et on en décrit treize autres cas. On considère que cette affection est une entité pathologique spécifique capable de provoquer une douleur lombaire.

On considère le diagnostic différentiel de l'ostéite condensante iliaque, surtout par rapport à la spondylarthrite ankylosante.

Sept cas, diagnostiqués au début comme ostéite condensante iliaque sont reconnus maintenant comme ceux de spondylarthrite ankylosante. Ils représentent un type de spondylite limitée ou abortive, plus fréquente chez les femmes.

Osteitis condensans ilii y su diferenciación de la espondilartritis anquilosante

Sumario

Se pasa en revista la afección conocida como osteitis condensans ilii y se describe trece casos más. Se considera que esta afección es una entidad patológica específica que puede causar un dolor lumbar.

Se considera el diagnóstico diferencial de la osteitis condensans ilii, particularmente respecto a la espondilartritis anquilosante.

Siete casos, inicialmente diagnosticados como osteitis condensans ilii, fueron luego reconocidos como ejemplos de esponsilartritis anquilosante. Estos representan un tipo de espondilartritis limitada o abortiva, más común en mujeres.

SHOULDER AFFECTIONS IN RHEUMATOID ARTHRITIS

BY

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Rheumatoid involvement of the shoulder seems to be, according to the literature (except Weil and others, 1951), relatively rare compared with the involvement of peripheral joints, but painful symptoms in this region are common. Our knowledge of the aetiological relationship of these symptoms to rheumatoid arthritis is scanty and there are few if any detailed studies.

We have therefore studied 277 cases of rheumatoid arthritis to determine:

(*a*) the incidence of shoulder affections in rheumatoid arthritis,

(*b*) the varieties of painful disorders and their aetiology.

Material and Methods

The material consisted of 277 unselected and hospitalized patients with a confirmed diagnosis of rheumatoid arthritis, of which 152 were women, 103 men, and 22 children. Shoulder symptoms were found in 94 women, 57 men, and eight children (159 cases; 57·4 per cent.). These cases were submitted to a detailed analysis by the method of Moseley (1953). The mean age of the total group was 32 years, and of those with shoulder symptoms 37·3 years.

Results

In the detailed analysis of the material, the following results according to the incidence and coincidence of several disorders were obtained (Table, overleaf).

(A) Rheumatoid Arthritis

(1) Scapulo-Humeral Joint.—This was affected in 41 women, 26 men, and eight children (total 75; 47·1 per cent.). The cases fell into three stages of development:

Stage I.—Early cases (8), typical symptoms being:

(*i*) slight limitation of movement of the affected joint;

(*ii*) moderate tenderness and pain in the joint;

(*iii*) soft crepitation in the joint;

(*iv*) negative *x*-ray findings, except for slight atrophy.

Stage II.—More advanced cases with severe lesions in the joints (65), typical symptoms being:

(*i*) limitation of movement in the shoulder joint. This was sometimes severe, though none showed complete ankylosing (bony or fibrous). Some cases had relatively free movement in the joint, despite grave changes in the bone structure.

(*ii*) tenderness and pain of variable degree;

(*iii*) in all cases at least soft crepitation and in many bony crepitation;

(*iv*) *x*-ray findings positive in all cases. All stages from slight subcortical atrophy to large bony erosions were found. In some long-standing cases there was a narrowed joint space and the humeral head was drawn up by scar tissue.

Typical bone erosion was found in 33 patients. This was located on the medial side of the major tubercle, and its size varied from a pinhead to the tip of the thumb (Fig. 1). The unusually large size of this erosion and in many instances its rapid develop-

Fig. 1.—Large bone erosion in medial side of major tubercle.

TABLE

COMBINATION OF LESIONS IN VARIOUS PATIENTS

Site of Lesions		(A)			(B)	(C)	(D)	(E)	(F)	(G)	(H)	(I)	(J)	(K)
(A) Rheumatoid Arthritis	Scapulo-humeral joint ..	51	1	2	5	2					1	1		12
	Acromio-clavicular joint ..	1												
	Sterno-clavicular joint ..	2									1			
(B) Tendinitis		5			4									4
(C) Rheumatoid bicipital tenosynovitis		2				4						1		2
(D) Sub-acromial bursitis							3		1					1
(E) Arthralgia of shoulder joint								16						
(F) Calcareous tendinitis							1		3					1
(G) Osteo-arthritis of scapulo-humeral joint										4		1		4
(H) Radicular symptoms in region of shoulder		1		1							1			1
(I) Sympathetic reflex dystrophy		1				1				1		1		1
(J) Periarthritis of shoulder joint													5	2
(K) Scapulo-costal syndrome		12			4	2	1		1	4	1	1	2	27

ment were caused by the fact that rheumatoid granulation tissue which has invaded the bone between the edge of the cartilage and the attachment of the capsule was in continual friction with the coraco-acromial arc. This explains the reluctance of these patients to hold the arm in abduction, and their liability to adduction contractures. *This erosion forms a contraindication to all kinds of forced physiotherapy.* Pendulum exercises, where the head of the humerus is drawn downwards by the weight of the arm, are the only suitable type.

In six cases in which there were typical severe changes in the humeral head, the patients were unable to maintain the passive abduction of the arm. The situation resembles that of a complete rotator cuff rupture, but these patients had not done any heavy work for many years.

This lack of abduction results from distension of the supraspinatus tendon, or destruction of its insertion.

Stage III.—Cases in which the disease has burnt out (two).

(2) Acromio-Clavicular Joint.—(One woman.) This symptom is most accurately discovered by an axillary *x*-ray projection.

(3) Sterno-Clavicular Joint.—(Two cases.) This affection, disturbing the function of the shoulder girdle, may give rise to shoulder pain.

(B) Tendinitis.—Both this and tenosynovitis are common in rheumatoid arthritis. Tendinous tissue is richly represented in the shoulder region and a high incidence of this affection is to be expected. Symptoms of tendinitis of the rotator cuff were found in thirteen cases (eight women and five men). The diagnosis was based on the following points:

(*i*) Local tenderness in the region of the affected tendon can be verified by testing the rotation of the shoulder joint against resistance. Accurate local diagnosis is important because of the good results that may be achieved by local hydrocortisone injections.

(*ii*) A characteristic painful jog* and soft crepitus can be felt by both patient and examiner when the swollen and tender portion of the cuff impinges upon, and then passes under, the acromion or coraco-acromial ligament.

(*iii*) Atrophy of the spinatus muscles soon develops as a result of inactivity, or probably as a result of rheumatic involvement of the muscle.

These symptoms are mainly the same as in the incomplete tear of the rotator cuff, though these rheumatoid patients gave no history of trauma. Degenerative changes caused by ageing did not play an important role in these investigations because of the low mean age (36 years) of these patients.

(C) Rheumatoid Bicipital Tenosynovitis was found in nine cases (seven women and two men). The chief symptoms of this condition are:

* Term used by De Palma (1950).

(*i*) pain in the anterolateral aspect of the shoulder which may radiate into the adjacent areas. This pain is aggravated by any movement in excess of the voluntary range of motion.

(*ii*) the painful arc syndrome is usually positive.

(*iii*) there is local tenderness in the region of the bicipital groove.

(*iv*) the following test has been found to be the most accurate in indicating the impairment of the bicipital gliding mechanism: *when passive movements of the shoulder are made in different directions, holding the elbow tightly flexed at 90°, the patient feels pain localized at the bicipital groove* (Fig. 2). This phenomenon is much more accurate than that described by Yergason (1931) wherein pain is localized at the bicipital groove when resistance is offered to supination of the forearm with the elbow flexed at 90°. It is also more reliable than that described by Lippmann (1943), wherein pain is felt in the bicipital groove when the tendon of the long head, held under tension, is displaced to one side and then suddenly released.

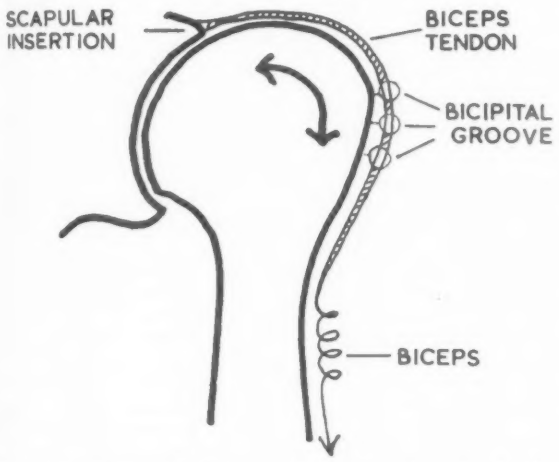

Fig. 2.—Diagram of movement of humerus (arrow), showing friction in bicipital groove.

The rheumatoid nature of the tenosynovitis in these patients was confirmed by biopsy in one case.

(D) Sub-Acromial Bursitis with Hydrops.—This was found in five cases (three women and two men). The chief symptoms of this condition are:

(*i*) depending on the size of the bursa, the tenderness may be felt over a larger area than the more localized tenderness due to tendinitis.

(*ii*) the painful arc syndrome is always positive.

(*iii*) the bursa can be felt in palpation as a fluctuating swelling lateral to the acromion.

(*iv*) if there is only a small amount of fluid in the bursa it is impossible to feel it by palpation in obese or muscular persons. Instead of fluctuation, a whirling sensation can be felt if the humerus is suddenly passively abducted or rotated so that the bursa impinges against the coraco-acromial arc. This sensation may continue for a short period after the movement has ceased.

(*v*) the bursal fluid is always of the same type as the fluid in rheumatoid arthritis joints (cell and protein contents).

In one case which was surgically explored, the wall of the bursa was enormously thick, and contained club-like synovial fringes. At the bottom of the bursa there was a mushroom-like exostosis, arising from the minor tubercle derived from the soft tissue covering of the bursal floor.

(E) Arthralgia of the Shoulder Joint.—This was found with no objective symptoms in eleven women and five men. These patients were young, their mean age being 31 years, and the duration of the symptoms was short. It is possible, therefore, that their symptoms can be regarded as prodromes of rheumatoid arthritis.

(F) Calcareous Tendinitis.—This was found in three women and two men. None of these cases was in an acute stage at the time of the investigation.

(G) Osteo-Arthritis of the Scapulo-Humeral Joint.—This was found in eight men and one woman, all of which had been heavy manual workers or had had traumata in the shoulder joint. One had had gonorrhoeal arthritis 12 years previously.

(H) Radicular Symptoms.—These were present in the region of the shoulder joint in four cases. This was due to osteo-arthritis in the cervical spine. One case had Klippel-Feil deformity with secondary osteo-arthritis at the only moveable part of the cervical spine.

(I) Sympathetic Reflex Dystrophy.—This was found in three women and two men. This condition had developed in one case after immobilization for tenosynovitis of the hand and one had osteo-arthritis of the cervical spine. Other coincidences are shown in the Table.

(J) Periarthritis of the Shoulder Joint (so-called "frozen shoulder").—This was found in four women and three men whose mean age was 50 years. Inflammatory changes in the soft tissues of the joint were definite. On the other hand, such changes in a rheumatoid joint may be due to inactivity.

(K) Scapulo-Costal Syndrome (Michele and others, 1950).—This was present in 43 females and twelve males. Typical signs of this condition are:

(*i*) pain, mostly localized in the upper scapular region, which may radiate to a large area in the upper extremity, back, chest, or neck. Headache is often present.

(*ii*) trigger points, usually round the scapula; secondary trigger points may develop at the radiation area.

(*iii*) irritation of the trigger point causes radiant pain.

(*iv*) paraesthesiae.

(*v*) impaired shoulder function.

(*vi*) anaesthesia of the trigger point removes symptoms.

This complex syndrome, until now inadequately interpreted, seems to be commonly combined, as a secondary symptom, with rheumatoid arthritis, as are all types of fibrositis. The elimination of this accessory syndrome, which fortunately responds to treatment, offers a welcome relief to the arthritis patient and facilitates his rehabilitation.

Summary

(1) Shoulder pain in connexion with rheumatoid arthritis is common. It was found in 57·4 per cent. of the 277 patients examined.

(2) Arthritis, tendinitis, and bursitis, due to rheumatoid affections, comprise the dominating syndrome. They were found in 50·9 per cent. of the different disorders discovered (total number of diagnoses 206).

(3) Many other symptoms, either independent, or secondary to rheumatoid arthritis, were found in 49·1 per cent., the most common (in 54·4 per cent.) being the scapulo-costal syndrome.

(4) Accurate analysis of the cause of shoulder pain in rheumatoid arthritis is a necessary condition for adequate treatment.

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Atteinte scapulaire dans l'arthrite rhumatismale
Analyse des 160 cas

Résumé

(1) Une douleur scapulaire associée à l'arthrite rhumatismale est fréquente. On l'a trouvé dans 57,4 pour cent des 277 malades examinés.

(2) L'arthrite, la ténosite et la bursite dues aux affections rhumatismales forment le syndrome prédominant. On les trouva dans 50,9 pour cent des différents troubles observés (nombre total des diagnostics: 206).

(3) On trouva beaucoup d'autres symptômes, soit independants, soit secondaires à l'arthrite rhumatismale, dans 49,1 pour cent des cas, le plus fréquent (54,4 pour cent) étant le syndrome scapulo-costal.

(4) Pour instituer un traitement approprié il est nécessaire d'étudier avec précision la cause de la douleur scapulaire dans l'arthrite rhumatismale.

Afecciones del hombro en la artritis reumatoide
Análisis de 160 casos

Sumario

(1) Un dolor escapular asociado á la artritis reumatoide es frecuente, habiéndose encontrado en el 57,4 por ciento de los 277 enfermos examinados.

(2) Artritis, tendinitis y bursitis debidas a las afecciones reumatoides forman el síndrome predominante, ya que fueron encontradas en el 50,9 por ciento de los varios disturbios observados (número total de diagnósticos: 206).

(3) Encontráronse muchos otros síntomas, sea independientes, sea secundarios a artritis reumatoide, en el 49,1 por ciento de los casos, siendo el más frecuente (54,4 por ciento) el síndrome escapulo-costal.

(4) Para poder instituir un tratamiento adecuado se necesita un análisis preciso de la causa del dolor escapular en la artritis reumatoide.

REITER'S SYNDROME AND CORTISONE

BY

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(RECEIVED FOR PUBLICATION FEBRUARY 24, 1954)

The three main features of Reiter's syndrome are conjunctivitis, polyarthritis, and urethritis, although the patient described by Reiter (1916) also had diarrhoea. The vast majority of reported cases have been seen in young adult males. It is thought that the following case may be of interest because the patient was an elderly female and her response to cortisone was disappointing.

Case Report

A Eurasian widow, aged 62, was admitted to the General Hospital, Penang, on November 5, 1952, with a history of 9 days' fever and dysuria followed by sore eyes and severe pain in the left wrist. For the previous 20 years she had been subject to attacks of "rheumatism". She described this as intermittent pains in the feet, knees, and back, lasting a few days or weeks but not accompanied by any joint swelling. The upper limbs were not affected. The "rheumatism" had not necessitated staying in bed. She had never suffered from dysentery. Nine days before admission there had been a sudden onset of "fever" with dysuria. The patient noticed "blood and pus" in the urine and this was confirmed by her family doctor. After 4 days, her eyes became sore and the left wrist painful, red, and swollen. During the next few days the dysuria gradually stopped but the severity of the other symptoms increased.

On admission, she appeared to be an intelligent woman obviously ill. She weighed 56 kg. The temperature was 100·2° F. She had purulent conjunctivitis, and there was marked tenderness and limitation of movement, with swelling, redness, and increased heat of the left wrist and first metacarpophalangeal joints. Physical examination was otherwise not remarkable. There was no vaginal or urethral discharge. No skin lesions, lymphadenopathy, or splenomegaly were observed. Urine examination showed many pus cells but culture was sterile.

Blood Examination.

No malaria parasites;
Haemoglobin, 65 per cent.;
Leucocytes, 14,600 per c.mm. with normal differential count;
Sedimentation rate (Westergren), 107 mm./hr;
Uric acid, 3·6 mg. per cent.;
Kahn test negative.

Thereafter serial leucocyte counts were within normal limits.

During the next 3 weeks she was given penicillin eye drops, sulphatriad (total 20 g.), and sodium salicylate (6 g. daily). After a week her conjunctivitis and pyuria had cleared up but the general condition and arthritis became worse. Pyrexia continued, her weight fell by 2 kg., and the arthritis spread to the joints of the left fingers and elbow, right thumb, wrist, knees, and toes, with, in most joints, marked tenderness, limitation of movement, swelling, increased heat, and redness. *X* rays of chest, wrists, and fingers showed no abnormality. Sodium salicylate was increased to 12 g. daily for 4 days with slight though definite decrease in arthritic manifestations.

On November 29 cortisone was started, 100 mg. twice daily, then 50 mg. twice daily by intramuscular injection. All other drugs were stopped. The cortisone was stopped on December 23 after 2·6 g. had been given. During this 3½-week period there was a gradual improvement in her general and arthritic condition. She felt better and her appetite improved. The pain and swelling in many of the joints diminished. Objectively, however, the response was far from dramatic. Intermittent pyrexia continued, there was no gain in weight, and serial sedimentation rates consistently ranged above 100 mm./hr. Moderate improvement in tenderness, swelling, and movement was noted in many joints, but in a few, these signs became more marked. After the cortisone was stopped, the arthritis again became worse, and within a week was much the same as when cortisone was started. She was given 3 g. aspirin daily and weekly intramuscular injections of 50 mg. myocrysin (total, 320 mg.). During 3 weeks of this regime, there was no significant change. On January 13, 1953, the daily dose of aspirin was increased to 8 g., but after 3 days it was reduced to 4 g. on account of vomiting and tinnitus.

Thereafter, there was a gradual but consistent improvement. She became afebrile, and on February 7, her only complaint was slight pain in the wrists. The blood sedimentation rate was still above 100 mm./hr. The dosage of aspirin was reduced and she was discharged from hospital on February 18, when there was moderate thickening and limitation of movement of both the left wrist and the left elbow joint. On July 9, 1953, she felt quite well apart from occasional twinges of pain in wrists and fingers, and had resumed her occupation of sewing to supplement her income. She weighed 58 kg. and looked well. There was full painless movement

of all joints and slight thickening of the left wrist. The B.S.R. was 50 mm./hr. *X* ray of wrists and fingers was again normal.

Comment

The cause of Reiter's syndrome is not known. Dysentery and a venereal aetiology have both been suggested, but both can be confidently excluded in the case reported. As the disease is generally self-limiting, the effects of treatment are difficult to assess. Ogryzlo and Graham (1950) described three cases as responding dramatically to ACTH (40 and 100 mg. daily) and cortisone (one course by injection totalling 4·4 g. in 23 days, later an oral course of 3·5 g. in 17 days). Joint pain and tenderness disappeared within 3-10 days. The B.S.R. fell to normal in two cases, and from 110 to 39 mm./hr in the third. On withdrawal of hormones, relapse was rather prompt in all cases, although the returning symptoms were usually not so severe and the subsequent course was one of improvement. Evang (1952) was not so enthusiastic; she reported a case in which cortisone was administered intramuscularly for 6 weeks (total 5 g.). There was a definite decrease in joint pain and swelling, but slight pain persisted. The joint symptoms recurred after discontinuation of cortisone but were not as severe as before the treatment. She concluded that cortisone did not have any certain effect on the duration of the disease.

In the case reported above, the response to cortisone did not appear to differ significantly from the response to aspirin, and in view of the natural history of the syndrome, it is doubtful if either drug had any effect on the disease.

Kellgren and others (1952) reported cases of rheumatoid arthritis which responded only partially or not at all to cortisone. Three patients had withdrawal deterioration although administered hormone had had no apparent effect.

Subsequently, Kersley and others (1952) published a case in which lack of response to cortisone could not be explained by inadequate dosage, failure to reach the target organ, or lack of conversion to hydrocortisone, and the fault was presumed to lie primarily in the end-organ or affected tissues.

Summary

A case of Reiter's syndrome in an elderly woman is reported. The observed response to cortisone was poor.

I wish to thank the Director of Medical Services, Malaya, for permission to publish this paper.

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Syndrome de Reiter et Cortisone

RÉSUMÉ

On rapporte un cas de syndrome de Reiter chez une femme âgée. On observa que la reponse à la cortisone fut faible.

Sindrome de Reiter y la cortisona

SUMARIO

Se relata un caso de síndrome de Reiter en una mujer de edad avanzada. Se observó que la respuesta a la cortisona fué escasa.

CORRESPONDENCE

THE USE OF COLCHICINE IN GOUT*

To the Editors, *Annals of the Rheumatic Diseases.*

SIRS,

The article "Intravenous Colchicine in the Management of Gouty Arthritis" by W. Graham and J. B. Roberts, which appeared in your issue of March, 1953 (1), states that:

> In June, 1949, a French preparation for parenteral administration became available to us, and treatment of a series of patients was begun. At that time no references were found in the English literature to the use of colchicine intravenously in the treatment of gout . . .

Readers should be referred to the paper entitled "Gout—a Prevalent Arthritic Disease", which was read by Solomon and Stecher, of Cleveland, Ohio, at the Eastern Sectional Meeting of the American Congress of Physical Therapy on April 5, 1941 (2). In the discussion which followed this valuable paper, Prof. Russell L. Cecil stated *inter alia*:

> I do not know of any more dramatic treatment than to give a patient suffering from acute gout an intravenous injection of colchicine . . .

Prof. Cecil later informed me that he was using ampoules of sodium salicylate and iodine with Colchicine No. 1, manufactured by Eli Lilly and Co., of Indianapolis, U.S.A., and the South African Lilly representative supplied me with this preparation early in 1942.

My personal experience with intravenous colchicine, appeared in April, 1949, in a paper entitled "The Gouty Diathesis" (3), in which I stated that the first dose is usually 1 mg. and the following doses only 0·5 mg. It is therefore inaccurate to state that there was "no reference in the English literature to the use of colchicine intravenously before June, 1949".

Because much smaller doses than those used by Graham and Roberts have given such dramatic results and because of the cumulative effect of colchicine, I am strongly against the intravenous administration of the heroic 3-mg. dose advocated by these authors. I have never seen any "irritant effect on the gastro-intestinal tract", although I have now given about 5,000 intravenous injections containing colchicine to patients of different ages and sexes. I have never as yet exceeded the 1 mg. and 0·5 mg. doses, however, even in patients whose tolerance of colchicine was well known to me.

Yours faithfully,

NATHAN FINN

76 Harrow Road,
Yeoville,
Johannesburg, Union of South Africa.

May 12, 1953.

* It is regretted that so long a delay has occurred in the publication of this letter.

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BOOK REVIEW

VIII Congreso Internacional de Enfermedades Reumaticás. 1953. Pp. 114. *Rev. esp. Reum.*, vol. 5, no. 4, p. 153. Sociedad Española de Reumatismo, Barcelona. (60 *pesetas*).

This review covers the papers given at various sessions of the Congress held at Geneva in 1953. The subjects dealt with, in the main, were: connective tissue and rheumatism, steroid hormones, the surgery of the hip-joint, rehabilitation of chronic patients, and the use of Butazolidin; a final session was devoted to a variety of subjects. Short summaries are given of each paper presented.

It is quite obvious that much research has gravitated recently to studying the structure and biochemistry of connective tissue. These problems are extremely complicated and various papers were given to try to elucidate the factors governing the growth and pathology of collagen, elastic tissue, etc. This work, in its initial stages, is mostly grounded in theory but may well bear considerable fruit in the near future.

With regard to the hormones, P. S. Hench stresses the importance of assessing each patient individually. Of his "systems" the one of small doses over long periods seems to be preferred; he still uses gold in suitable cases. E. G. L. Bywaters and others have found little difference in the results of treating rheumatic fever with ACTH, cortisone, or salicylate. Most authors agree that small intra-articular doses of hormone are decidedly beneficial, especially in the knee-joint. Hormones are thought to be of little value in degenerative arthritis.

The reports on Butazolidin were very favourable. Some consider that the remissions last longer than those with ACTH. The numerous complications should not preclude its use. It is effective in gout but especially so in rheumatoid arthritis and ankylosing spondylitis. Modern opinion is that it does not act by stimulating the pituitary-adrenal mechanism.

Plastic operations on the hip-joint seem to produce good results in 60-80 per cent. of cases; R. J. Judet considers severe pain one of the main indications for operation, but believes in persevering with conservative measures prior to surgery.

The papers on rehabilitation were along the usual lines.

PAUL B. WOOLLEY.

EMPIRE RHEUMATISM COUNCIL

SEVENTEENTH ANNUAL REPORT

The seventeenth annual report of the Empire Rheumatism Council was presented by the Chairman, Dr. W. S. C. Copeman, at the Annual General Meeting held on April 28, 1954, at the Royal College of Surgeons. The Chairman first recorded with regret the deaths of Dr. Mervyn H. Gordon, Vice-President, and Sir Walter Kinnear, formerly Chairman of the Finance Committee. He next paid tribute to the retiring Chairman, Lord Horder, saying how pleased the members of the Council were to know that Lord Horder had consented to accept the office of "Emeritus Chairman".

Three matters deserved the special attention of members. First, a deputation led by Lord Horder had waited upon the Minister of Health on May 19, 1953. Secondly, the Council had been invited to submit evidence to the Ministry of Labour's Committee of Inquiry into the rehabilitation and settlement of disabled persons (Piercy committee), and a memorandum had been drawn up by a special sub-committee. Thirdly, a chair of rheumatology, the first in the Commonwealth, had been financed at Manchester University, and Dr. J. H. Kellgren, a member of the Council, had been appointed to this professorship.

Research.—The work on steroid metabolism at the Council's Maclean Laboratory at the Hospital of St. John and St. Elizabeth, London, terminated in March, 1953, when Dr. A. A. Henly left to take up another appointment. His final report on his tenure of the "Roche Fellowship in Biochemistry" described the results obtained during clinical trials of ACTH, cortisone, and other steroid substances. The findings in general were consistent with the conclusion that such changes in steroid metabolism as were found were the results of metabolic abnormalities associated with the disease process and that primary adrenal dysfunction was not a causative factor in the development of rheumatoid arthritis.

The Council's Laboratory would continue to be used by an Empire Rheumatism Fellow, and was likely to be engaged for the next two or three years on special projects, for which new equipment and apparatus was being obtained.

The work at Westminster Medical School, carried out by Dr. J. D. Billimoria in association with Prof. N. F. Maclagan and Dr. F. Dudley Hart, had produced a number of new simple analogues of cortisone, and some of these had shown a slight cortisone-like activity in biological tests. The discoveries appeared to be of fundamental interest, and this work, which was being continued under the auspices of the Governor's Discretionary Fund of Westminster Hospital, would be watched with great interest by the Council.

Dr. J. L. Porter had reported on the work done during his 2-year tenure of an "Elizabeth Macadam Fellowship"; although his tentative conclusions regarding the treatment of ankylosing spondylitis by radiotherapy were of considerable interest, further evidence was required before his hypothesis could be accepted, and it was considered that the publication of a paper based on this work would be premature. Work on the excretion of steroid metabolites in urine during radiotherapy was being continued in the Rheumatic Unit at the Northern General Hospital.

Dr. B. F. Matthews, also an "Elizabeth Macadam Fellow", had continued his work on biochemical change in ageing cartilage at the Canadian Red Cross Memorial Hospital, Taplow, Bucks, under the direction of Dr. E. G. L. Bywaters. He had found that with the degenerative joint change of advancing age, there was a decrease in the mucopolysaccharide content compared with the fibrillar collagen framework. It seemed probable that this loss of mucopolysaccharide was a direct expression of the attrition undergone by such joints.

Dr. J. M. Tweed, the first "Philip Gray Fellow", had carried out basic research into the long-term treatment of rheumatoid arthritis at the West London Hospital, which was about to be published. Dr. Tweed had now returned to New Zealand. Dr. J. H. H. Glyn who had been appointed as his successor, had previously spent a year in New York University (Bellevue Hospital) working with Dr. J. J. Bunim, and would shortly be completing a research project then begun.

Two other E.R.C. Fellows had been appointed to carry out specific research. Dr. J. K. Norymberski was appointed on November 1, 1952, for a period of 3 years to work under the direction of Dr. H. F. West at the Chemical Research Laboratory of the Sheffield Centre for the Investigation and Treatment of Rheumatic Diseases. During the past year work had been concluded (in collaboration with Dr. C. J. W. Brooks) on the oxidation of cortico-steroids with sodium bismuthate. This investigation had led to the development of:

(*a*) an analytical method for the simultaneous determination of formaldehydogenic and 17-ketogenic steroids,
(*b*) a routine procedure for the estimation of 17-ketogenic steroids in urine.

Judging by the results so far obtained, the latter provided a reliable means of assessing the adrenal

output of glucocorticoids. It had been further found (in collaboration with Miss Sermin) that sodium bismuthate brings about the oxidative fission of steroid glucuronides; this finding led to the development of a method for the differential estimation of urinary steroid conjugates. Work had been begun (in collaboration with Dr. Jean McKenna) on the chemistry of steroid sulphates. Mr. G. Gibson and Mr. R. D. Stubbs had also assisted in these investigations. Dr. Norymberski had not only provided the means for further research, but had also found a new and much needed steroid assay of immediate practical value for the assessment of pituitary-adrenocortical function and for the control of ACTH therapy.

The other E.R.C. Fellow, Miss I. H. M. Muir, had been appointed from April 1, 1953, to work under the direction of Prof. Pickering at St. Mary's Hospital, Paddington. The original aim of her research was to investigate soluble collagen-like proteins in normal and diseased states. Her previous work had shown that these soluble collagens were precursors of collagen itself, and it was expected that even in adult human tissues, these proteins would be present in appreciable amounts. However, no soluble collagens could be found even in young adults, unless the tissues had been considerably denatured, which rendered valueless any deductions which could be made, and this work had therefore been abandoned. It was then decided to attempt to verify a report in the literature (*Lancet*, 1952) that experimental arthritis could be produced by sensitization to chondroitin sulphate previously incubated with streptococci. The chondroitin sulphate in the report was heterologous. If this experiment could be repeated using homologous polysaccharide, then the aetiology of rheumatoid arthritis might be explained by assuming an auto-sensitization of the individual to his own connective tissue polysaccharides. A repetition of the experiment with a preparation of homologous chondroitin sulphate containing no detectable amounts of protein, produced no arthritis, and no formation of antibody to the sulphate could be conclusively demonstrated. Attention had now been turned to examining some enzymological aspects of connective tissue metabolism, which might yield information useful to the understanding of rheumatic diseases.

Treasury sanction had been obtained by the Council to transmit a financial contribution to Dr. E. Wittkower in support of his "Study of Rheumatoid Arthritis in two Contrasting Communities" at McGill University, Canada. A recent progress report outlined the long-term comprehensive programme of psychosomatic and psychological research upon which he and his colleagues had been engaged. The tests done so far showed that concentration on hospital patients gave a faulty view of:

(*a*) the premorbid personality of patients suffering from rheumatoid arthritis,
(*b*) the disturbing effect of the illness on the family situation,
(*c*) the impact of the illness on community service.

In order to obtain a more representative sample of patients (short of carrying out a demographic survey, for which enormous funds would be required) it was now intended:

(1) to follow up the contact which had been established with the Victorian Order of Nurses,
(2) to approach other welfare agencies and rehabilitation centres,
(3) to trace through the co-operation of the Canadian Arthritis and Rheumatism Society, homebound patients who never attended any of the hospital clinics,
(4) to survey patients with rheumatoid arthritis who were working in industry, and not therefore greatly incapacitated. It was hoped to obtain the co-operation of some of the larger industries for this part of the project.

The Cortisone/Aspirin Trial had been begun in the nine specially selected centres (associated with the Council in England and Scotland) as follows: West London Hospital Medical School; Arthur Stanley Institute, Middlesex Hospital; Post-Graduate Medical School; Royal Free Hospital; Westminster Hospital; Royal Mineral Water Hospital, Bath; Sheffield Centre for the Investigation and Treatment of Rheumatic Diseases; General Infirmary, Leeds; Northern General Hospital, Edinburgh. During the first 9 months of 1953 a course of cortisone therapy had been started with 49 patients on the lines agreed by the Trials Committee, and a detailed analysis of the result would be undertaken after all the patients had completed one year's trial.

The generous offer of a 6-months' supply of Compound F by Messrs. Merck and Co. Inc., New Jersey, had been gladly accepted, and the following ten centres had been selected to undertake clinical investigations: West London Hospital Medical School; Arthur Stanley Institute, Middlesex Hospital; Post-Graduate Medical School; Royal Free Hospital; Westminster Hospital Medical School; Royal Mineral Water School, Bath; Sheffield Centre for the Investigation and Treatment of Rheumatic Diseases; General Infirmary, Leeds; Northern General Hospital, Edinburgh; Royal Infirmary, Manchester. The trials had begun in some centres in July, 1953, and the Chairman hoped to be able to report upon the conclusion of the trials in 1955.

A request had been received for financial aid to investigate a sample of each type of case apt to be referred to a Department of Physical Medicine, and the contribution such a department could make to the problem of treating rheumatic disease in the community. The appropriate Committee of the Council had decided to recommend that this investigation should be subsidized.

Applications for financial aid from the Council's Hormonal Research Equipment Fund had been granted in cases where applicants were unable to obtain apparatus or equipment from other sources. Certificates of good order had been received from all those centres where equipment had been purchased by the Council for such research.

Education.—A week-end lecture-demonstration course had been held at the Arthur Stanley Institute, Middlesex Hospital, in November, 1952.

The Council participated in the B.M.A. Scientific Exhibition at Cardiff, July, 1953. The stand, staffed by members of the Council's medical committees, afforded an opportunity to demonstrate to medical practitioners (by notes, diagrams, *x*-rays, and specimens) a general outline of current views on rheumatoid arthritis, spondylitis, osteo-arthritis, and gout. Rheumatism centres throughout the country combined in the demonstrations. A publication, "Notes on Arthritic Conditions", compiled by the Council, was available at the stand for free distribution.

A special Coronation Lecture on "The Concept of Collagen Disease", delivered by Professor Sir Henry Cohen on July 2, 1953, at the Royal Society of Medicine, attracted a large and distinguished audience.

At a Symposium on Phenylbutazone ("Butazolidin"), held at the Royal Society of Medicine in November, 1953, the chief guest speakers were Dr. Otto Steinbrocker (New York), and Prof. Domenjoz (University of Saarbrücken).

The Council would shortly be publishing a "Handbook on Rheumatoid Arthritis", for issue initially to all rheumatism centres in Great Britain and to the medical advisory committees of the Regional Hospital Boards. This handbook would be available free to general practitioners, and application for copies might be made to the General Secretary of the Council.

The first meeting of the new Expert Committee for Rheumatic Diseases of the World Health Organization was held in Geneva in August, 1953, when the Chairman had the honour to represent the United Kingdom and was appointed Chairman of the Expert Committee.

The Council had continued to subsidize the Heberden Society in its educational programme of lectures and demonstrations, and the Society, under its President, Lord Horder, had had a very successful year. Clinical meetings organized by the Society and held at the Middlesex Hospital, by kind permission of the Dean; at University College Hospital; at the Devonshire Royal Hospital, Buxton; and at 11 Chandos Street, London, had been very well attended.

The *Annals of the Rheumatic Diseases*, the official medium through which the activities of the Empire Rheumatism Council, the Heberden Society, the British Branch of the European Council, and kindred organizations in Europe and America were made known to the rheumatological world, had published during 1953 accounts of the proceedings of the Annual Meeting of the American Rheumatism Association, and those of the Dominions Councils affiliated to the Empire Rheumatism Council, the 8th Congress of the International League, held in Geneva in August, the Symposium on Fibrositis, held at the B.M.A. Annual Meeting in Cardiff in July, and the European Symposium on Cortisone, held at Milan in September. The sterling value of the *Annals* could not be too highly emphasized, and it was felt that everybody desirous of keeping himself abreast of the latest techniques of rheumatism research, treatment, and education should become a regular subscriber.

Commonwealth.—The Council continued to receive from its affiliated branches the reports of proceedings at their Annual General and Committee Meetings, and these showed the level at which rheumatism research and education was developing in those Dominions.

The Council had also been privileged to welcome several members, notably from Canada and New Zealand; they wished the Dominion affiliated organizations well, assuring them that they were always ready to place their experience and advice at their disposal.

OFFICERS, 1954-55

The following executive officers were re-elected:

Chairman:	Dr. W. S. C. Copeman.
Vice-Chairman:	Lord Webb-Johnson.
Emeritus Chairman:	Lord Horder.
Hon. Medical Secretary:	Dr. Oswald Savage.
Deputy Medical Secretary:	Dr. R. M. Mason.

Visit of the Minister of Health

The Minister of Health, the Rt Hon. Iain Macleod, P.C., M.P., visited the rheumatism wards and the Empire Rheumatism Council's laboratory at the Hospital of St John and St Elizabeth on May 17, 1954. He was accompanied by Lord Horder, Dr W. S. C. Copeman, and Sir Daniel Davies.

NEW YORK RHEUMATISM ASSOCIATION

ANNUAL MEETING, 1954

The Annual Meeting of the New York Rheumatism Association was held at Cornell University Medical College, New York, on April 20, 1954. Dr. Robert M. Lintz presided and the following papers were presented:

Standards for Evaluation of Chronic Musculo-Skeletal Pain. By J. H. Irvine (*Welfare Hospital*).

Group Therapy with Patients with Rheumatoid Arthritis. By E. Rudd and V. Foster (*French Hospital*).

Effect of Long-Continued Cortisone Therapy on Bone Marrow of Rheumatoid Arthritis Patients. By H. H. Tillis (*Beth Israel (Newark) Hospital*).

Phenylbutazone in Rheumatoid Arthritis: Long-Term Evaluation. By S. J. Bosch, M. E. Ehrlich, and Otto Steinbrocker (*Hospital for Joint Diseases*).

Simultaneous Administration of Anti-Coagulants and Cortisone. By W. B. Rawls (*Polyclinic Hospital*).

New Modification of the Streptococcus Agglutination Reaction in Rheumatoid Arthritis. By C. M. Plotz, F. Plishuk, and M. Wolf (*Mt. Sinai Hospital*).

Inhibition of Sensitized Sheep-Cell Agglutination Reaction in Rheumatoid Arthritis, and its Role in the Agglutination Test. By M. Ziff, P. Brown, J. Badin, and Currier McEwen (*Bellevue Hospital, Third Division*).

Research in Rheumatic Diseases at the Royal Free Hospital. By E. T. D. Fletcher (*London, England*), by invitation.

The Rheumatoid Cripple: Is He Salvable? By E. W. Lowman (*Institute of Physical Medicine and Rehabilitation*).

Clinical Physiology and Pathology of the Temporo-Mandibular Joint. L. L. Schwartz, D.D.S. (*Presbyterian Hospital*), by invitation.

Use of Intravenous Trypsin in Rheumatoid Arthritis. By C. M. Plotz (*Kings County Hospital, State University Division*).

Studies on Metabolism of Adrenal Cortical Steroids in the Synovial Cavity in Rheumatoid Arthritis. By H. Wilson, R. Fairbanks, Currier McEwen, and M. Ziff (*Bellevue Hospital, Third Division*).

Mobilization of Gouty Tophi. By A. B. Gutman and T. F. Yü (*Mt. Sinai Hospital*).

Role of the General Practitioner in Rheumatoid Diseases. By R. Klein (*Greenpoint Hospital*).

Modification of the Niacin Furfuryl Test by DPN in Rheumatoid Arthritis. By G. G. Haydu (*Goldwater Memorial Hospital, Second Division*).

Three Cases of Rheumatoid Arthritis aggravated by Pregnancy and controlled by Cortisone. By I. Gould and M. Wolf (*Mt. Sinai Hospital*).

Osteo-Arthritis of Cervical Spine as a Source of Headaches and Facial Pain. By E. Neuwirth (*Great Neck, N.Y.*).

RHEUMATOLOGY IN BRAZIL

It is regretted that Professor Jacques Houli's new appointment was incorrectly described in the last issue (*Annals*, 1954, **13**, 71). Professor Houli holds the Chair of Rheumatology at the Post-Graduate School of Medicine of the Medical Society of Medicine and Surgery, Rio de Janeiro. Another Chair of Rheumatology, an even earlier foundation, is held by Professor Pedro Nava at the Policlínica do Rio de Janeiro.

ABSTRACTS

This section of the ANNALS *is published in collaboration with the two abstracting Journals,* ABSTRACTS OF WORLD MEDICINE, *and* OPHTHALMIC LITERATURE, *published by the British Medical Association.*

The abstracts selected for this Journal are divided into the following sections: Acute Rheumatism; Chronic Articular Rheumatism (Rheumatoid Arthritis, Osteo-Arthritis, Spondylitis, Miscellaneous); Disk Syndrome; Gout; Non-Articular Rheumatism; General Pathology; ACTH, Cortisone, and other Steroids; Other General Subjects. At the end of each section is a list of titles of articles noted but not abstracted. Not all sections may be represented in any one issue.

The section "ACTH, Cortisone, and other Steroids" includes abstracts and titles of articles dealing with steroid research which, although not directly concerned with the rheumatic diseases, may make an important contribution to knowledge of the scope and *modus operandi* of steroid therapy.

Acute Rheumatism

Hormone Therapy in Acute Rheumatic Carditis in Children. (Hormonothérapie dans la maladie de Bouillaud chez l'enfant.) BARDIER, A., BOUISSOU, H., and METHOT, —. (1953). *Presse méd.*, **61**, 1040. 10 refs.

The authors compare the results of treatment at the Clinique Médicale Infantile, Toulouse, of 28 children with acute juvenile rheumatic carditis, of whom thirteen were given salicylates and fifteen ACTH (corticotrophin) or cortisone. Details of dosage, types of cases, and follow-up results are given. In the authors' opinion acute attacks of carditis, unless very severe, can generally be treated successfully by the usual salicylate therapy, but recurrences are not infrequent and valvular lesions often persist. Of those treated with the hormones, three, all severe cases, died, but the other twelve responded favourably, although no change was seen in established valvular lesions. It is concluded that treatment with ACTH or cortisone is preferable to that with salicylates, particularly in severe attacks of rheumatic carditis, but that it must be started early in the disease if it is to be effective; if this can be done, permanent cardiac damage may be avoided. Hormone therapy is not advised for patients with chronic valvular lesions, nor as interval treatment between attacks. *Kathleen M. Lawther.*

Treatment of Rheumatic Carditis in Children with Hormones and Salicylates. (Il trattamento ormonico-salicilico della cardite reumatica del bambino.) GELLI, G., and MENICHINI, G. (1953). *Arch. ital. Pediat.*, **16**, 85. Bibl.

The combination of salicylates with cortisone or ACTH (corticotrophin) in the treatment of rheumatic fever allows the use of smaller doses of each substance; it seems probable also from experimental evidence that the two drugs enhance one another's action, and that their use together may prevent the development of adrenal atrophy.

At the Paediatric Institute of the University of Pisa, thirteen children with rheumatic fever or chorea have been treated in this way, eight during their first attack. Doses of 25 mg. ACTH or 50 mg. cortisone were given daily for 3 weeks, and the dose was then halved for a further 3 weeks. Simultaneously, 4 to 6 g. sodium salicylate was administered daily, this dose also being halved later. In addition, penicillin and streptomycin were given during the whole period of treatment, partly because of a belief in the initial infective nature of the disease and partly to combat any increased risk of infection resulting from the hormone therapy. A low-salt diet with added ascorbic acid was given, and the usual measures for the relief of cardiac failure were instituted when necessary.

All the patients improved rapidly, the most striking effects being noted on the extracardiac manifestations of the disease: one patient with chorea, for instance, lost his symptoms altogether within 10 days. No danger was encountered from fluid retention, and three patients in heart failure—one seriously ill—all responded satisfactorily. The effect of the combined therapy on the cardiac lesions was much more difficult to assess: although the signs of endocardial involvement did not progress, in only two patients did they entirely disappear, and this during their first attack. As might be expected, myocarditis and pericarditis appeared to be more susceptible to treatment than endocarditis, but the electrocardiogram was of little help as a guide to improvement because of the changes produced by the electrolyte disturbances accompanying treatment.

The authors conclude that while the course of the disease was much shortened and, although several were extremely ill initially, no patient in this series died, it cannot yet be said that a form of treatment has been found which materially alters the results of cardiac involvement in rheumatic fever. *A. Paton.*

Non-Specific Myocarditis in Acute Rheumatic Fever. SAPHIR, O., and LANGENDORF, R. (1953). *Amer. Heart J.*, **46**, 432. 7 figs, 14 refs.

Doubting the role attributed to the Aschoff bodies in the aetiology of myocarditis and in the causation of myocardial failure in acute rheumatic fever, the authors, working at the (U.S.) Armed Forces Institute of Pathology, Washington, D.C., studied microscopically the

myocardium in 22 cases in which death was due to acute rheumatic disease and in which there was clinical evidence of myocarditis. Electrocardiographic records were available for twelve of the cases. Only cases were examined in which typical Aschoff bodies were present in the interstitial tissue; in all cases interstitial lymphocytic infiltrations were also found, both in association with and apart from the Aschoff bodies. In eighteen cases there were in addition circumscribed foci of myonecrosis which, when cellular reaction had occurred, resembled Aschoff bodies. It is suggested that these appearances may explain the recent revival of the theory that the Aschoff body arises from damaged muscle. The authors regard these necrotic foci as due to a non-specific myocarditis and relate the changes in the electrocardiogram to its occurrence. *A. C. Lendrum.*

Correlation between Active Rheumatic Lesions in the Left Auricular Appendage and Elsewhere in the Heart. KUSCHNER, M., and LEVIEFF, L. (1953). *Amer. J. med. Sci.*, **226**, 290. 6 refs.

The significance of the presence of Aschoff bodies in the auricular appendage of forty rheumatic hearts was studied post mortem at Bellevue Hospital (Columbia University), New York. In five of the cases commissurotomy had been performed for mitral stenosis. It is suggested that if Aschoff bodies are present in the appendage there are likely to be signs of activity elsewhere in the heart, and that the absence of Aschoff bodies from the appendage does not exclude the possibility of signs of activity elsewhere. Of the eighteen hearts with appendicular thrombus, seventeen were from cases of auricular fibrillation, and fourteen of them on histological examination showed no signs of activity in the form of Aschoff bodies, auriculitis, or acute verrucous endocarditis, singly or in combination. *A. C. Lendrum.*

Reactivation of Rheumatic Fever following Mitral Commissurotomy. SOLOFF, L. A., ZATUCHNI, J., JANTON, O. H., O'NEILL, T. J. E., and GLOVER, R. P. (1953). *Circulation* (*N.Y.*), **8**, 481. 10 figs, 8 refs.

The authors draw attention to a syndrome that they have noted as a sequel to mitral valvotomy. The symptoms, mainly precordial pain and fever, have been noted in 43 out of 179 cases of mitral stenosis treated by commissurotomy (24 per cent.) and are regarded as something separate from the ordinary complications that may arise in the course of any thoracic operation. In 24 additional cases the patient complained of pain, coming on after discharge from hospital, which was of a similar nature but unaccompanied by fever.

The onset of pain is sudden and may take place anything from 10 days to a month after operation. It is gripping and vice-like over the pericardium, radiates over a wide field, may last several weeks, and may recur. Associated with the pain is a variable degree of fever, which is accompanied by toxaemia, weakness, and sweating. Other features, such as psychosis, heart failure, and arthritis, may be added to the picture, the cardiac symptoms being the most important. The most likely explanation is that there has been a reactivation of the rheumatic process; the 179 cases included in this study formed part of a consecutive series of 183, four having been excluded because the operation was followed immediately by acute rheumatic fever. Biopsy of the left atrial appendage was taken at operation in 37 of the 43 cases in which the syndrome subsequently developed. Aschoff bodies were identified microscopically in fifteen (40·5 per cent.) of these, but also in a practically identical percentage of cases in which the syndrome did not occur.

The fate of the 43 patients who developed the syndrome was varied: three died, two developed hemiplegia, three became psychotic, and five went into permanent auricular fibrillation. Of the remaining 29, the majority require as much medical attention as they did before the operation, or more.

The authors do not discuss the implication of these findings for the selection of patients for operation beyond insisting on the desirability of excluding patients with clinically active rheumatism and commenting on the difficulty of recognizing this condition.

T. Holmes Sellors.

Rheumatic "Activity" as Judged by the Presence of Aschoff Bodies in Auricular Appendages of Patients with Mitral Stenosis. II. Clinical Aspects. MCNEELY, W. F., ELLIS, L. B., and HARKEN, D. E. (1953). *Circulation* (*N.Y.*), **8**, 337. 1 fig., 15 refs.

The histological examination at the Thorndike Memorial Laboratory (Harvard Medical School) of biopsy specimens from the auricles of 183 patients undergoing operation for mitral stenosis at Boston City Hospital showed that 45·4 per cent. contained typical Aschoff bodies, although all patients had been carefully selected as showing no clinical evidence of rheumatic activity. The incidence of Aschoff bodies declined with age, 73 per cent. of patients aged 20 to 30 years showing the bodies as contrasted with only 8 per cent. of those over 50. It was also found that Aschoff bodies were much less frequent when auricular fibrillation was present (17 per cent. of cases) than when the heart rhythm was normal (76 per cent.). This difference was independent of the age of the patient and the duration of the disease. The results of clinical tests for rheumatic activity or active carditis, such as estimation of the erythrocyte sedimentation rate and antistreptolysin titre, and electrocardiography could not be correlated with the incidence of Aschoff bodies.

The authors suggest that although their results do not disprove the generally accepted view that the presence of Aschoff bodies indicates a state of rheumatic activity, it must be concluded, if this view is correct, that the current clinical tests for rheumatic activity are too crude to detect a smouldering rheumatic carditis. *H. F. Turney.*

Electrophoretic Analyses of Plasma or Serum Proteins of Rheumatic-Fever Patients in relation to Stages of Disease. JACKSON, R. L., KELLY, H. G., SMITH, E. K., WANG, P., and ROUTH, J. I. (1953). *Amer. J. Dis. Child.*, **86**, 403. 1 fig., 27 refs.

Recent evidence seems to show that the increased susceptibility of some patients to rheumatic fever may

be related to the immunological status of the blood. In this study, carried out at the Children's Hospital, Iowa City (State University of Iowa College of Medicine), the authors investigated by electrophoresis the changes in serum and plasma protein levels of 77 children with "definite rheumatic fever" treated by "standard non-specific methods of therapy", and five patients with chorea but without other manifestations of rheumatic fever. The plasma or serum, diluted with 3 volumes of a barbiturate buffer (*p*H 8·6, ionic strength 0·1), was dialysed in the cold for 3 days, and electrophoresis was carried out in the Longsworth modification of the Tiselius apparatus.

The results were considered in nineteen separate groups or subgroups, according to the stage of the disease, the presence of decompensation, and the presence of mild intercurrent infections or exacerbations at the time the serum sample was obtained. [The criteria by which these patients were assigned to the various groups are not further specified.] Patients with a remittent type of disease and those with chorea alone formed two separate subgroups, but any one patient might appear more than once in any particular group or once in each of several groups; thus, the study was based on 205 separate samples of serum or plasma, each patient being counted a mean of 2·2 times. The results of the estimation of the total protein content and the percentage composition of the various components are given, standard deviations being shown for each group. Some over-all clinical data for the various groups are also included, for example the percentage of patients with fever, or with signs of active carditis, the mean and range of the erythrocyte sedimentation rate, and the mean and range of the interval from onset of the disease, these values being compared with those in a group of 31 normal children as reported by Knapp and Routh (*Pediatrics*, 1949, **4**, 508). Briefly, it was found that during recovery there was a progressive increase towards normal in the proportion of albumin, a marked decrease towards normal in the proportion of alpha-2 globulin, fibrinogen, and gamma globulin, a less marked fall in alpha-1 globulin and gamma′ globulin, but no significant change in beta globulin. There was good correlation of the erythrocyte sedimentation rate (Westergren) with the values of albumin (correlation coefficient (r) = $-0{\cdot}55$), and of alpha-1 and alpha-2 globulin, fibrinogen, and gamma globulin ($r = +0{\cdot}43$ to $0{\cdot}56$) but no correlation with beta globulin ($r = +0{\cdot}04$). In cases with decompensation there was a tendency to elevation of the alpha-2 globulin and a decrease in beta globulin values compared with those in patients in the same clinical stage but without decompensation. In those with chorea but with a normal sedimentation rate, there was a significant departure from normal values of the albumin, alpha-2 globulin, and to a lesser extent, gamma globulin levels. It is thought that the changes in the serum albumin level may be compensatory to the changes in globulin level, while the change in the values of alpha-1 globulin may be related to the increase in C-reactive protein and of the alpha-2 globulin to increase in serum mucoprotein. The obscuring of the true gamma′ globulin values by the incorporation of gamma′ globulin in the fibrinogen peak is discussed.

[As the groups differed in composition, except for the occasional presence of certain individuals, they are not strictly comparable, especially as some subjects furnished two or more samples of serum for inclusion in the same group.] *E. G. L. Bywaters.*

Aureomycin in the Prophylaxis of Rheumatic Fever. McVAY, L. V., and SPRUNT, D. H. (1953). *New Engl. J. Med.*, **249**, 387. 5 figs, 44 refs.

Aureomycin was given prophylactically to 23 patients who had had rheumatic fever, twelve similar patients serving as controls. Of the treated group eighteen (average age 17 years) had had an attack of rheumatic fever in the preceding 5 years, as compared with eight (average age 16 years) of the control group. A dose of 250 mg. aureomycin was given 30 minutes or one hour before breakfast and again 2 hours after the evening meal. The period of observation ranged from 2 to 20 months, averaging 9 months in the treated group and 11 months in the control group. Rheumatic fever recurred in one of the 23 treated patients and in four of the twelve controls during the investigation. A reduction in the incidence of respiratory infections of approximately 50 per cent. was observed in the treated group. Side-effects of the antibiotic were minimal.

[This series is too small and the observation period too short for firm conclusions to be drawn. The patients were mostly from an older age group, in which recurrences are normally less frequent than in young children. Penicillin is less expensive than aureomycin and should therefore be used as a routine until some other drug is shown to be more effective in preventing a recurrence.] *R. S. Illingworth.*

Chorea Minor. Preliminary Report on Six Patients treated with Combined ACTH and Cortisone. SCHWARTZMAN, J., ZAONTZ, J. B., and LUBOW, H. (1953). *J. Pediat.*, **43**, 278. 6 figs, 18 refs.

This is a preliminary report on the simultaneous use of ACTH and cortisone in the treatment of chorea minor. The trial was carried out at the Flower and Fifth Avenue Hospitals and the Metropolitan Hospital, New York, in six cases of the disease in children between 6 and 11 years old. The combined therapy was continued until symptoms disappeared, which occurred in from 8 to 48 days. As regards side-effects, moon-face was noted in all cases and hypertension in three. When untoward symptoms appeared the dosage of the hormones was at once reduced. There was an absence of rebound phenomena at the end of treatment. In three cases latent urinary infection with positive urine cultures was discovered, leading the authors to suggest that the renal tissues of growing children may be vulnerable to the action of these hormones.

In view of the small number of cases in this series the conclusions drawn are cautious and tentative, but the authors, comparing their own results with those of others who have used one or other of these hormones, not in combination, consider that the combined administration

of ACTH and cortisone has given "rather better" results. At this stage of the study it is not claimed that "hormone therapy is the preferred and acceptable one for this condition", and it is admitted that further study and investigation are required. *Charles McNeil.*

Rheumatic Fever in Infancy. (Fiebre reumatica en el niño.) KREUTZER, R. (1954). *Rev. port. Pediat.*, **17**, 23.

ACTH in Severe Cases of Rheumatic Disease in Children. (ACTH w ostrych postaciach choroby gośćcowej u dzieci.) WILKOSZEWSKI, E., KIELIOTIS, W., and ANTONIEWICZ, E. (1953). *Pediat. pol.*, **28**, 1209.

Withdrawal Effects of Cortisone in the Therapy of Rheumatic Fever in Young Adults. DANIELS, R. S., GULOTTA, G. A., and PETERSON, W. L. (1954). *U.S. armed Forces med. J.*, **5**, 176. 8 refs.

Effect of Cortisone and Corticotropin on the Erythrocyte Sedimentation Rate and Duration of Fever in Rheumatic Fever. (Verkan av cortison- och corticotropinbehandling på sr och feberperioden vid febris rheumatica.) KALLIOMAKI, L., and OKA, M. (1954). *Nord. Med.*, **51**, 296. 2 figs, 15 refs.

Treatment of Prophylaxis of Streptococcal Infections for Prevention of Rheumatic Fever. HOUSER, H. B. (1953). *J. Mich. med. Soc.*, **52**, 1289. 17 refs.

Preventive Aspects of the Treatment of Rheumatic Fever. (Aspetti preventivi nel trattamento della malattia reumatica.) BALLABIO, C. B. (1954). *Reumatismo*, **6**, 87. 1 fig.

Rheumatic Scarred Heart. IBRAHIM, M., and ABDEL RAHMAN, M. L. (1953). *J. Egypt. med. Ass.*, **36**, 623. 1 ref.

Rheumatic Fever and Rheumatic Heart Disease in Egypt. LOTFY ABDEL RAHMAN, M., IBRAHIM, M., SOROUR, A., EL-SHERIF, A., and EL RAMLY, Z. (1953). *J. Egypt. med. Ass.*, **36**, 611. 2 refs.

Chronic Articular Rheumatism
(Rheumatoid Arthritis)

Cortisone and Rheumatoid Disease. WEST, H. F., and NEWNS, G. R. (1953). *Lancet*, **2**, 1123. 6 refs.

It is known that cortisone in a daily dosage of 100 mg. or more has a profound effect on the symptoms and signs of rheumatoid disease, but unfortunately doses greater than 75 mg. a day can rarely be maintained for many months without serious complications. The present investigation was undertaken at the Centre for the Investigation and Treatment of Rheumatic Diseases, Sheffield, to provide a definite answer to the question whether the oral administration of cortisone acetate in doses of 50 to 75 mg. per day over a long period favourably affects the course of the disease.

To this end 27 patients were given cortisone acetate in the above dosage for an average of 19 months, and the results compared with those in a similar group of 27 patients who did not receive cortisone. (A further three patients treated with the hormone died after 9 to 13 months and were excluded from the study.) The effects on the fundamental disease process were assessed by objective determination on six points: stiffness of joints after rest; need for analgesics; physical abilities; erythrocyte sedimentation rate; anaemia and plasma protein level; and the radiographic changes. In addition, observations on weight, strength of grip, and blood pressure, as well as the results of various laboratory investigations, are recorded. It is pointed out that an over-all average leucocytosis, with a stable lymphocyte count, is a feature to be taken into account when considering whether the treatment given had been physiological or not.

Of the three deaths, two could not be ascribed to the cortisone treatment, but may have been hastened thereby, while the third patient died from haemorrhage from an internal lesion of polyarteritis nodosa.

The conclusion is reached that long-continued cortisone therapy for rheumatoid disease is not to be recommended. The observations were not, however, considered necessarily to exclude the possibility that corticosteroids play an important part in the pathogenesis of rheumatoid disease, or that prolonged administration of cortisone may be of benefit in certain types of the disease. It is, however, considered that there is no theoretical reason why this hormone should have any curative effect in this disease [as distinct from the peripheral blocking of symptoms], and that long-continued suppression of adrenal production of hydrocortisone constitutes a real danger to the subsequent effectiveness of the defence mechanisms against normal and abnormal stresses.

Harry Coke.

Observations on the Use of Cortisone and ACTH in Rheumatoid Arthritis. CLARK, W. S., TONNING, H. O., KULKA, J. P., and BAUER, W. (1953). *New Engl. J. Med.*, **249**, 635. 8 figs, 13 refs.

Observations are reported from the Massachusetts General Hospital, Boston, on the treatment with cortisone or ACTH (corticotrophin) of 52 patients ranging in age from 2½ to 62 years suffering from rheumatoid arthritis of 1 to 29 years' duration. A number of patients received both drugs, but at different times.

A total of 42 courses of cortisone were administered, with major subjective improvement in 31 (74 per cent.) and major objective improvement in 16 (38 per cent.). Similar degrees of improvement occurred in 11 (60 per cent.) and 4 (22 per cent.) of the eighteen courses of ACTH given. In addition to the hormones, the patients also received basic treatment consisting of rest, aspirin, hydrotherapy, and active exercises. No prolonged remission of the disease was observed after withdrawal of the hormones, and relapse was rapid in most cases. Histological examinations of tissue made during treat-

ment showed a decrease in oedema and inflammatory cellular infiltration, with some reduction in fixed cellular hypertrophy and hyperplasia.

The most serious side-effects encountered were psychosis, for which cortisone treatment had to be stopped in eight cases and ACTH treatment in six, oedema, and severe potassium loss. The authors found that the effective use of the hormones in this series was limited by the hazards of hypercorticism, and emphasize that no precautionary measure is known which will obviate the need for constant observation. In their view the most valuable effect of the drugs is to decrease pain and stiffness, with consequent improvement in function.

Oswald Savage.

A New Form of ACTH Therapy for Rheumatoid Arthritis. (Über eine neue Form der ACTH-Therapie bei der rheumatischen Polyarthritis.) PROSIEGEL, R., GOELKEL, A., and FUCHS, U. (1953). *Dtsch. med. Wschr.*, **78**, 1494. 34 refs.

The effect of an intravenous drip infusion containing both ACTH (corticotrophin) and insulin was studied at the University Medical Clinic, Munich, on eleven patients suffering from polyarthritis of varying degree and was found to equal that of a much higher intramuscular dose of ACTH alone; further, only small doses of ACTH were found to be necessary to prevent relapses once maximum improvement had occurred. It was also observed that many of the frequently described symptoms following withdrawal of ACTH therapy, such as severe exacerbation of the arthritis and mental depression, did not occur after treatment with ACTH combined with insulin.

Hypoglycaemia due to the insulin was a side-effect difficult to control; the addition of glucose to the infusion to counteract this also seemed to increase the beneficial effects of the therapy. One patient who continued to complain of pain despite the administration of large amounts of ACTH was relieved of symptoms by the addition of insulin and glucose. Although the urine was regularly tested for sugar and frequent blood sugar estimations were performed, in most patients no marked changes were found, most of the glucose added to the infusion being completely absorbed, and only after a large amount had been given did traces appear in the urine.

The levels of corticosteroids in the urine paralleled the clinical improvement, and in most patients the levels were as high with ACTH and insulin as they were with much larger doses of ACTH alone. Insulin alone or small doses of ACTH alone did not always lead to a rise in urinary steroid level, and Ringer's solution given intravenously as a control produced no alteration in the steroid excretion. The possibility of insulin acting as a stimulator of the synthesis of biologically active hormones from the adrenal glands is discussed.

Robert Hodgkinson.

Intravenous Iron in Rheumatoid Arthritis: Possible Prognostic Factors. JEFFREY, M. R. (1953). *Brit. med. J.*, **2**, 912. 3 refs.

In an attempt to determine the factors of possible prognostic value in the treatment of the anaemia which often accompanies rheumatoid arthritis, a course of iron was given intravenously to each of fifty patients with rheumatoid arthritis, in this investigation reported from the Rheumatism Research Unit, Bath. The total dose of iron given was calculated (on the basis that each 100 mg. iron raises the haemoglobin level by 4 per cent.) to be more than adequate to raise the haemoglobin to 100 per cent. (14·8 g./100 ml.). In fifteen patients the haemoglobin level became normal, in 22 it was improved, and in the remaining thirteen it was unchanged.

The results of the determination of various blood components in these three groups of patients were then analysed to determine if there were any prognostic factors which might be of use in forecasting the response to intravenous iron therapy. It was observed that a normal haemoglobin level was always achieved if the erythrocyte sedimentation rate was below 30 mm./hr, or if microcytosis, gross hypochromasia, or a raised total iron-binding capacity of the serum was present. But the haemoglobin level also became normal in some cases in which none of these features was present. The degree of activity of the rheumatoid arthritis, or the levels of plasma iron, serum protein, and the free erythrocyte protoporphyrin were therefore concluded to be of no prognostic value.

K. C. Robinson.

Diagnosis and Treatment of Still's Disease. DIMSON, S. B. (1954). *Rheumatism*, **10**, 18. 1 fig., 27 refs.

Combined Vaccine Treatment and Chemotherapy in Rheumatoid Arthritis. (A terapeutica combinada da artrite reumatóide.) SUAREZ, GONZALEZ (1954). *J. Méd.* (*Porto*), **23**, 411.

Infiltration with Procaine of the Splanchnic Nerves and Gasserian Ganglion in Rheumatoid Arthritis. (La infiltración novocaínica de los esplácnicos y del semilunar y reumatismo crónico progresivo inflamatorio.) GRABER-DUVERNAY, J., GERVAY, F., VAN MOORLEGHEM, J., and BLANCH TERRADAS, F. (1953). *Arch. cardio-rheum. hisp.*, **1**, 222. 2 refs.

Rheumatoid Arthritis after the Age of 55. (La polyarthrite chronique evolutive apres l'age de 55 ans (P.C.E. tardive et P.C.E. sénile).) ISÉMEIN, L., and REDON, M. (1953). *Rev. Rhum.*, **20**, 877.

(Osteo-Arthritis)

Arthrosis of the Shoulder. (L'arthrose de l'épaule.) COSTE, F., LAURENT, F., and CHAOUAT, Y. (1953). *Rev. Rhum.*, **20**, 675. 15 figs, 7 refs.

As osteo-arthritis of the scapulo-humeral joint is relatively uncommon—in two series quoted, only 18 instances were found in 763 cases of painful shoulder—the authors give a short clinical account of the condition. It is found chiefly in elderly subjects, and is usually secondary to a congenital malformation of the humeral head, to an old osteochondritis, or to severe trauma. The clinical features, namely, dull pain in the shoulder, atrophy of the deltoid and supra- and infra-spinatus

muscles, with restriction of movement, are similar to those observed in the late stages of the more common scapulohumeral periarthritis, in the slowly progressive shoulder stiffness of senile tuberculosis of the joint, in rheumatoid arthritis, and in the arthritis of ankylosing spondylitis.

The differential diagnosis is discussed, and the several varieties of the condition are illustrated by typical radiographs. The treatment recommended is the administration of vitamins, calcium, or compounds of iodine and sulphur, and in some cases mud packs and radiotherapy have proved useful. Mobilization of the shoulder is considered to be dangerous (but the reasons for this are not stated). *Kenneth Stone.*

Composition of Articular Cartilage in Osteo-Arthritis. Changes in Collagen : Chondroitin-Sulphate Ratio. MATTHEWS, B. F. (1953). *Brit. med. J.*, **2**, 660. 6 refs.

In a previous paper (*Brit. med. J.*, 1952, **2**, 1295) the author suggested that an alteration in the collagen : chondroitin-sulphate ratio in cartilage occurred in the weight-bearing joints, the decrease in the ratio being due to an increase in chondroitin-sulphate which is a measure of the protecting matrix. In the present paper, from the Canadian Red Cross Memorial Hospital, Taplow, Bucks., he describes an investigation of damaged fibrillation cartilage and healthy cartilage in the knee-joint and patellar surface of the femur. The collagen : chondroitin-sulphate ratio was higher in fibrillar (degeneration) cartilage than in healthy cartilage. The author interprets this finding as indicating a slower rate of loss of collagen as compared with matrix substance, the loss or absence of matrix substance rendering the cartilage liable to greater damage and fissuring.

[The paper certainly opens up a chemical approach to the problem of osteo-arthritis.] *R. E. Tunbridge.*

Lactic Acid in the Treatment of Osteo-Arthritis. LAWRENCE, J. S. (1953). *Lancet*, **2**, 913. 7 refs.

The author reviews the literature of the treatment of osteo-arthritis by intra-articular injection of lactic acid. In his own study, carried out at the Rheumatism Research Centre, University of Manchester, he treated one hundred patients by standard methods of physiotherapy, but fifty of these received in addition intra-articular injections of lactic acid combined with procaine. The two groups were considered to be of similar severity, and assessment of the results was made after 3 and 6 months.

It was found that subjective and objective improvement occurred in equal numbers in both groups. The psychological effect of the injections did not seem to affect the results in the group receiving lactic acid. Similarly, the number of patients who were able to return to work was the same in both groups.

The author therefore concludes that the intra-articular injection of lactic acid is of no therapeutic value in osteo-arthritis. *W. Tegner.*

Treatment of Osteo-Arthritis. (Über die Therapie der Arthrosis deformans.) BUSCH, J. (1954). *Münch. med. Wschr.*, **96**, 284.

Arthritis of the Hip treated by Intra-Articular Injection in 130 Cases. (Cent trente cas de coxarthrose traités par injections intraarticulaires.) ORY, M. (1953). *Acta physiother. rheum. belg.*, **8**, 166.

Radiotherapy in Osteo-Arthritis. (Röntgen-therapie der Arthrosis deformans.) PANNEWITZ, G. VON (1953). *Strahlentherapie*, **92**, 375. 4 refs.

Prevention, Detection, and Treatment of Osteo-Arthritis. BRAILSFORD, J. F. (1954). *Rheumatism*, **10**, 2. 5 refs.

Nature and Treatment of Osteo-Arthritis. HEMBROW, C. H. (1953). *Alfred Hosp. clin. Rep.* (*Melbourne*), **3**, 39. 1 ref.

(Spondylitis)

Radiological Observations on the Sacro-Iliac Joint in 100 Cases of Rheumatoid Arthritis. (Osservazioni radiologiche sulle articolazioni sacroiliache di 100 malati di poliartrite cronica primaria.) ROBECCHI, A., and CAPRA, R. (1953). *Reumatismo*, **5**, 298. 15 refs.

While it is generally agreed that typical changes in the sacro-iliac joints are found in all but very early cases of ankylosing spondylitis, opinions differ as to whether such changes are associated with this disorder alone, some authors alleging that they occur in a certain percentage of cases of rheumatoid arthritis, and that ankylosing spondylitis is not a separate entity but merely a particular manifestation of rheumatoid arthritis.

In the study here reported from the Maggiore Hospital, Turin, the pelves of 71 female and 29 male patients aged from under 20 to 70 years, with rheumatoid arthritis, were examined radiologically. In 76 cases the sacro-iliac joint was judged to be normal. In the remaining 24 cases the joint showed various changes, consisting in most cases in marginal sclerosis and a narrowed and indistinct joint space. Exceptionally, the joint margins were irregular and the joint space was interrupted by bony bridges, but none showed complete disappearance of the joint line. The changes were not related to the duration of the disease, to the number of other joints involved, or to the involvement or not of the hip-joints, but there appeared to be some relationship with involvement of the lumbar spine. In no case did the changes correspond to the typical evolutionary phases of ankylosing spondylitis, the changes in the sacro-iliac joint of most of the patients being unilateral, a finding considered rare in ankylosing spondylitis. Other workers have reported similar changes in the sacro-iliac joints of non-arthritic subjects, particularly women who have had multiple pregnancies; also such changes are not uncommon in elderly subjects, in whom they are due to degeneration.

The authors conclude from their study that the radiological changes observed in the sacro-iliac joints of rheumatoid arthritic patients are not significant, as they do not vary substantially from those in non-arthritic subjects of the same age and sex, and also do not present the characteristics generally considered typical of ankylosing spondylitis. They maintain, therefore, that the two diseases are distinct entities. *W. D. Nichol.*

Changes in the Periarticular Soft Tissues in Ankylosing Spondylitis. (Sulle alterazioni delle parti molli periarticolari nella spondilosi rizomelica. Osservazioni istopatologiche.) PICCHIO, A. (1954). *Reumatismo*, **6**, 1. 9 figs, 38 refs.

(Miscellaneous)

New Method of Treatment for Arthritis. FINZI, N. S. (1953). *Brit. J. Radiol.*, **26**, 488.

This paper describes an empirical method of treatment of chronic arthritis which the author has found "very valuable". It consists in the application of deep *x* rays to the cervical and lumbo-sacral regions for arthritis of the upper and lower limbs respectively. For the upper limb a surface dose of 75 to 80r, gradually reduced to 55 or 60r, is given to the back of the neck at 200 kV, with F.S.D. of 40 cm., a Thoraeus filter, and a field of 15 × 15 cm. For the lower limb, a field of 20 × 15 or 20 × 12 cm. is used, extending from D 12 to S 3, at 50 cm. F.S.D., the dose given being 80 to 100r, reduced gradually to 65 or 70r. The addition of small doses to the affected joints seems to be of value—a depth dose of 60r, reducing to 45r, being advised. Treatment is given weekly (though this may not be the optimum interval) and most patients experience an increase of pain after 12 to 48 hrs. The course is continued for 12 to 16 weeks, or until reaction ceases; results are better in the presence of reactions. Courses can be repeated two or three times, as the skin doses are so low. If there is no response after six doses, treatment is discontinued. A few cases in which striking results were obtained, including disappearance of gross synovial thickening of the knee joints, are quoted [but no attempt is made at a statistical evaluation of results]. The mode of action is not understood, though it has been attributed (without supporting evidence) to some effect on the sympathetic nerves or ganglia with consequent changes in blood supply to the joints. *J. Walter.*

Treatment of Articular Rheumatism by Inhibition of Hyaluronidase. (Therapie rheumatischer Gelenkerkrankungen durch Hyaluronidasehemmung.) GIGGLBERGER, H. (1953). *Dtsch. med. Wschr.*, **78**, 1439. 48 refs.

An investigation previously carried out at the University of Würzburg into the action of "Venostasin" (an extract of horse-chestnut containing glycosides of the flavone group) suggested that the drug inhibits hyaluronidase *in vivo*. It therefore seemed likely that it would be found useful in the treatment of cases of arthritis in which the viscosity of the synovial fluid is increased, since it has been suggested that the beneficial effects of ACTH are largely due to its power of inhibiting hyaluronidase. Moreover, in rheumatic fever the blood has been found to contain increased quantities of non-specific inhibitors of hyaluronidase as well as specific antibody.

The results are now reported of the treatment of eleven cases of chronic arthritis with daily intravenous injections of 10 ml. Venostasin for 12 days. Most of the cases treated were of rheumatoid arthritis which had proved resistant to other forms of therapy. There were no unpleasant side-effects. All the patients benefited to a greater or lesser extent, although the erythrocyte sedimentation rate appeared to be uninfluenced. In every case capillary permeability, as estimated by Landis's method, was diminished and capillary resistance, as estimated by Hecht's method, was increased, and this phenomenon was in direct relation to the amount of clinical improvement obtained. The beneficial effect of the drug on the capillaries is ascribed to its inhibition of hyaluronidase. *D. Preiskel.*

Dermatomyositis. Report of 26 Cases in Children with a Discussion of Endocrine Therapy in Thirteen. WEDGWOOD, R. J. P., COOK, C. D., and COHEN, J. (1953). *Pediatrics*, **12**, 447. 8 figs, 32 refs.

The natural history of dermatomyositis and the value in treatment of the administration of endocrines are discussed with reference to 26 cases seen at the Children's Medical Center and Massachusetts General Hospital, Boston, between 1916 and 1952. The ages of the patients ranged from 2 to 11 years. At the time of the report sixteen of the patients were still alive; seven of the ten who died had had the disease for less than 2 years. The diagnosis was confirmed by biopsy in 23 cases; no other diagnostic aid was of any value. Generally the onset was insidious, with weakness and tiredness as the predominant symptoms. In 23 cases the face was involved.

The authors point out that vigorous physiotherapy and orthopaedic treatment, to prevent crippling contractures and deformities and to correct them once they occur, are the only effective measures available at the present time. Corticotrophin (ACTH) or cortisone by intramuscular injection was tried in the acute stage of the disease and appeared to be of some value; testosterone was then given sublingually, in the hope that the improvement would be maintained. Symptomatic benefit was observed in all the thirteen so treated. The authors recommend a full dose of ACTH or cortisone at the beginning of treatment, the patient being placed on a low-sodium diet supplemented with potassium. This is continued for 2 to 3 weeks, when the dose of hormone is gradually reduced; testosterone is then administered and continued for several months. *Wilfrid Gaisford.*

Treatment of Lupus Erythematosus with Mepacrine (Atebrin). HARVEY, G., and COCHRANE, T. (1953). *J. invest. Derm.*, **21**, 99. 10 refs.

Mepacrine was tried in the treatment of patients with lupus erythematosus at the Royal Infirmary, Glasgow, the series comprising twenty patients who had not previously been treated for the condition and 42 who had failed to respond to other therapeutic measures. Only twelve of the patients in the first group responded satisfactorily, while in 25 of the patients in the second group the response was considered good. In nearly all the patients, however, there was a relapse after withdrawal of the drug, a much higher relapse rate than that observed with bismuth and oxophenarsine hydrochloride (Mapharside). A good temporary response was also obtained in

three patients with subacute and one patient with acute lupus erythematosus. Exfoliative dermatitis developed in one patient, lichenoid dermatitis in three patients, and hyperkeratosis of palms and soles in two. Proguanil hydrochloride (Paludrine) and chloroquine were each given to ten patients. The former was without effect, but the response in two of the patients given chloroquine was excellent, although one of these subsequently relapsed.

The percentage of satisfactory results in this series was 59·7, as compared with 73·5 in a series of 117 cases treated with bismuth and 66·2 in a series of 56 treated with oxophenarsine. *John T. Ingram.*

Erythema Exudativum Multiforme. Its Association with Viral Infections. WOMACK, C. R., and RANDALL, C. C. (1953). *Amer. J. Med.*, **15**, 633. 5 figs, bibl.

It is first pointed out that there are several syndromes which are now generally regarded as unusual manifestations of erythema multiforme, first described by Hebra in 1866; these include the so-called Stevens-Johnson syndrome, the ectodermosis erosiva pluriorificialis of Rendu, dermatostomatitis as described by Baader, the mucosal respiratory syndrome of Stanyon and Warner, Behcet's syndrome, ulcus vulvae acutum of Lipschutz, and Reiter's syndrome. No single specific cause of erythema multiforme is known; it appears likely that it is an allergic manifestation to a number of different agents.

The authors, after briefly reviewing the literature on the relationship of erythema multiforme to virus infections, report a case seen at the Vanderbilt University Hospital, Nashville, Tennessee, in which the virus of herpes simplex was isolated. The patient, a 19-year-old white woman, developed generalized lesions of herpes simplex infection which at one stage were indistinguishable from the lesions of erythema multiforme. In spite of intensive treatment over a period of 44 days in hospital the patient died from the disease.

In the authors' view sufficient evidence is available to indicate that the virus of herpes simplex is concerned in the pathogenesis of at least some cases of erythema multiforme. *H. R. Vickers.*

Cardiac Output in Osteitis Deformans. HOWARTH, S. (1953). *Clin. Sci.*, **12**, 271. 7 refs.

A previous report from the Postgraduate Medical School of London (Edholm and others, *Clin. Sci.*, 1945, 5, 249) described the investigation of cardiac function in a case of osteitis deformans, in which the signs of a hyperkinetic circulation with a greatly increased cardiac output were found. In the present paper the findings are reported in thirteen further cases. Cardiac output was measured by right-heart catheterization and was found to be above normal limits, ranging from 7·2 to 13·3 litres per minute in the five patients with the most active and extensive osteitis. Cardiac output was normal in all cases in which skeletal involvement was less than 35 per cent. and the plasma alkaline-phosphatase level less than 45 units per 100 ml. The extent to which the skeleton is involved by active disease, it is suggested, may be of greater significance than the plasma alkaline-phosphatase level in this connexion. In one case of Paget's disease in which the previous history suggested a high cardiac output the result during an inactive phase was normal.

(Details of the method used for assessing the volume of bone involved relative to that of the whole skeleton are given in an appendix.) *G. W. Csonka.*

Studies on the Peripheral Circulation in Osteitis Deformans. EDHOLM, O. G., and HOWARTH, S. (1953). *Clin. Sci.*, **12**, 277. 9 figs, 9 refs.

Studies of the peripheral circulation were carried out at the Postgraduate Medical School of London on eighteen patients with active osteitis deformans (Paget's disease). The peripheral blood flow, measured with the venous occlusion plethysmograph, was found to be increased in 21 out of 23 limbs in which the underlying bone was affected, whereas in nineteen limbs in which the underlying bone was radiologically normal the blood flow was within normal limits. In six cases of active Paget's disease measurement of the blood flow through the humerus by a method previously described (Edholm and others, *Clin. Sci.*, 1945, 5, 249) gave higher values than those recorded in normal control subjects and in a case of inactive Paget's disease. In two cases in which the bone marrow was presumed to be highly active there was also an increase in bone blood flow. The skin temperature was raised in areas directly overlying bones with active disease. In tests on two patients an intravenous injection of adrenaline was found to decrease the blood flow in the affected limbs, whereas the flow was increased in normal limbs, this being attributed by the authors to construction of the blood vessels of the diseased bone.

Bone biopsy and dissection of affected limbs at necropsy confirmed the increase in vascularity of bone in the active phase of osteitis deformans and its absence in the inactive phase and, together with the radiographic appearances, suggested that the greater part of the increased blood supply passes through the periosteal plexus rather than the nutrient artery. *G. W. Csonka.*

Value of Radiology in the Diagnosis and Management of Pyogenic Osteitis in Childhood. NELIGAN, G. A., and WARRICK, C. K. (1953). *J. Fac. Radiol.* (*Lond.*), **5**, 112. 10 figs, 6 refs.

The authors report their observations on 103 consecutive cases of acute pyogenic osteitis and four of primary chronic osteitis of the long bones seen in children admitted to the Royal Victoria Infirmary, Newcastle-upon-Tyne, since June, 1948. A simple classification based on the clinical picture is proposed.

In older children a severe clinical condition was found to be accompanied by marked radiological changes, but in clinically mild cases it was unusual to see any bone destruction, even when treatment was started late. In the severe acute cases the radiological changes were of no practical help in diagnosis as they appeared too late; the time of first appearance of these changes was unaffected either by the stage at which penicillin treatment was started or by the dosage of the antibiotic. In the

mild cases, however, the *x*-ray changes were of considerable value, as in these cases it was often impossible to be certain of the diagnosis on clinical grounds alone. In newborn and very young infants the clinical diagnosis may be delayed or difficult in both the mild and severe types; in the authors' cases bone changes were already present in the initial radiograph in eleven out of thirteen cases. In primary chronic osteitis, radiological changes were of course always present when the patient was first seen, and the problem was usually one of differential diagnosis. Of the four cases of secondary chronic osteitis, only one showed definite radiological evidence of persistent or renewed infection; in this respect clinical evidence was regarded as being more reliable.

In deciding on the best management of these cases the authors found that the radiological information was valuable in all cases, and in their 65 severe cases of acute osteitis it was a vital factor. Although the time to stop the administration of penicillin was always decided on clinical grounds, the radiological findings were of the greatest value in deciding when extensive surgery was necessary and the important question of when to allow unrestricted movement of the affected limb. The criterion for the latter was the first appearance of recalcification in areas previously showing progressive decalcification.

In the radiological diagnosis of osteitis in the newborn the problem of the double contour arises; this is briefly discussed and the authors agree that this appearance has a physiological cause and is not a manifestation of disease. The problem of deciding when to allow unrestricted movement is complicated by the decalcification resulting from disuse. For this reason the period during which a limb was splinted was kept to the minimum in this series. *John H. L. Conway-Hughes.*

Abdominal Topography in Relation to Senile Osteoporosis of the Spine. DENT, R. V., MILNE, M. D., ROUSSAK, N. J., and STEINER, G. (1953). *Brit. med. J.*, **2**, 1082. 2 figs, 8 refs.

In this investigation of the cause of loss of height in old persons, carried out at Crumpsall Hospital, Manchester, the authors made a radiological and anthropometrical study of 340 subjects (152 men and 188 women) whose average age was 68. (They [rightly] point out that as most of the subjects were chronic invalids, the results cannot be applied to old people in the general population.) In all subjects the "pelvi-costal ratio" was determined, this being defined as the ratio of the distance between the subcostal and supra-iliac lines to the subject's total length. In 54 patients (22 men and 32 women) there was an abnormally low pelvi-costal ratio (less than 1 to 100), in four of these the ratio actually being negative, that is, the subcostal line was lower than the supra-iliac line.

This group of 54 was therefore compared with a similar number, comparable as to age and sex, selected at random from the remaining 286 subjects, and subjected to a full radiological examination of the lumbar and dorsal spine, the following measurements being particularly considered:

(1) the angle between the lower ribs and the anterior border of the lower dorsal spine,
(2) the degree of lumbar lordosis expressed as an angular measurement,
(3) the length of the lumbar spine,
(4) the portion of the lumbar spine occupied by the intervertebral disks, and
(5) the degree of spinal osteoporosis.

Radiologically, the ratio of the minimum height of a single accurately-centred vertebral body to the average of its anterior and posterior heights, was taken as a better index of the presence and degree of spinal osteoporosis than the radiological density, which may be considerably affected by other factors.

The authors conclude that the main factor involved in shortening of the costo-pelvic distance is the increased obliquity of the ribs, which is secondary, at least in part, to senile kyphosis; and further, that spinal osteoporosis is almost universal amongst elderly chronic invalids, and is severe when the pelvicostal ratio is less than 1 per cent. of the total body length. *P. D. Bedford.*

Analysis of the Radiological Findings in 20 Cases of Osteoblastic Osteogenic Sarcoma. BERGIN, J. H. E. (1953). *Brit. J. Radiol.*, **26**, 628. 5 figs, 8 refs.

It is first pointed out that the diagnosis of osteogenic sarcoma depends upon clinical, radiological, and pathological evidence, each of which is of fundamental importance, and that mistakes may occur if the diagnosis is based on only one of these.

As regards radiological examination, the author emphasizes the need for multiple films, taken with varying degrees of rotation of the limb, and for films taken with different penetration to show the soft tissues in addition to bone detail. Serial films should be obtained with the same technique after an interval of some weeks or months. He analyses twenty cases of osteogenic sarcoma selected from the Bristol Bone Tumour Registry. In fifteen of these the clinical, radiological, and pathological findings were typical. Of the five patients with atypical signs and symptoms, three survived for a long time after treatment, one of them being free from any sign of recurrence for 6 years, when metastases developed in the lung.

The author suggests that the prognosis is best in cases which are typical histologically, but atypical clinically and radiologically. The tumour in these cases is probably of low malignancy, and a relatively long survival time is to be expected, whatever the treatment. In prognosis in these cases serial radiographs are of more help than histology. *D. E. Fletcher.*

Dupuytren's Contracture. A Radiotherapeutic Approach. FINNEY, R. (1953). *Lancet*, **2**, 1064. 6 figs, 10 refs.

In this paper from St. Thomas's Hospital, London, the author briefly discusses the different methods used in the last 50 years in the treatment of Dupuytren's contracture, particularly radiotherapy, and describes the results obtained in 25 cases by this means.

In Dupuytren's contracture pathological changes occur not only in the palmar fascia but also in the interstitial

connective tissue, where there is a lymphocytic infiltration and an increase in the number of capillaries. This is followed by absorption of fat and the formation of new connective tissue, leading, in advanced cases, to subcutaneous fibrosis. The characteristic change in the palmar fascia is a proliferation of the fibroblasts in the nodules of the contracture. Subsequently there occur deposition of collagen fibres, contracture of the collagen, and compression of the fibroblasts, producing an avascular contracted scar. The similarity of these changes to keloid formation is discussed.

As regards surgical treatment, the author states that the operation most widely employed today is radical removal of the palmar aponeurosis, but an examination of the literature shows a recurrence rate following this procedure of 15 to 35 per cent. In his series of 25 cases given radiotherapy a radium mould was applied for 8 hours a day for 8 days, and a dose of 3,000r was delivered during this time to the affected tissues. Subjective improvement was observed during the first month, and objective improvement was noted at about 2 months, becoming maximum at 6 months. The patients were followed up for 2 to 10 years. There was full functional recovery in eight patients, partial recovery in seven, and limited improvement in four; in six patients the condition was unchanged. In no case did the condition become worse or the contracture increase after treatment. The best results were obtained in early cases.

It is suggested that radiotherapy, alone or as a preoperative measure in late cases, should be given in cases of Dupuytren's contracture. *R. D. S. Rhys-Lewis.*

Arthrography of the Knee. (L'arthrographie du genou.) ARCHIMBAUD, J. (1953). *J. Radiol. Électrol.*, **34**, 623. 22 figs, 4 refs.

After trying various methods of arthrography of the knee-joint, employing air, contrast media, or double contrast, the author has come to the conclusion that simple arthrography, with air only, gives all the necessary information. In the method used at the Hôpital Saint-Luc, Lyons, 2 or 3 ml. of a 1 per cent. solution of procaine is injected in the depression behind the outer border of the patella almost as deep as the capsule. Through a small intravenous needle, inserted until it almost touches the articular surface of the patella, any effusion which may be present is completely aspirated. Some 80 to 100 ml. of air is then introduced, slight flexing movements being made to help dispersion while this is being done, and the suprapatellar pouch being palpated to make certain that the air is actually entering the joint space. Contrary to the practice of most workers, no Esmarch bandage is placed over the suprapatellar pouch. The patient is then turned on his face, and asked to flex and extend the joint several times. It is important for the centre of the *x*-ray beam to pass through the line of articulation; this is situated 4 cm. below the popliteal fold and this point should be marked with a skin pencil. The knee-joint is now flexed through 10° by allowing the leg to rest on the dorsal surface of the big toe. In order to bring the menisci into view, a valgus displacement must be made to expose the internal meniscus and a varus displacement for the external; three tangential views are taken for each meniscus. The intercondylar notch is examined by flexing the knee through 80° and using a ray tangential to the upper end of the tibia. When arthrography is completed the air is aspirated as completely as possible; any remaining air is absorbed within a few days, during which time the patient is advised to rest.

A persistent synovitis seldom results from arthrography, and indeed some hydrarthroses disappear rapidly after the examination. No case of purulent arthritis was encountered in the author's series of 400 cases.

The normal and pathological appearances to be expected in the joint are discussed in detail. The 400 cases are divided into two series: in the first (125 cases), 52 were operated on and there were six radiological diagnostic errors; in the second (275 cases), 68 were operated on and there were two radiological errors. In three cases, joints which were operated on in spite of normal radiological appearances were all found to be normal. *John H. L. Conway-Hughes.*

Horizontal Tomogram in Rheumatology. Studies of the Knee in Anatomical Preparations and Normal Subjects. (Le tomogramme horizontal en rhumatologie. Études sur le genou: pièces anatomiques et sujet normal.) SÈZE, S. DE, DEBEYRE, J., DJIAN, A., and LÉVY-LEBHAR, J. P. (1953). *Rev. Rhum.*, **20**, 467. 23 figs, 1 ref.

The authors describe an experimental study of the possibilities of horizontal tomography as applied to bones and joints, with particular reference to rheumatic conditions. The technique employed resembles that of Vallebona, but the authors use a tube with a very fine focus (0·3 mm.), and the importance of using such a tube for obtaining clear images is strongly stressed.

They then go on to describe and illustrate in detail the results of examinations of a number of anatomical specimens of the knee, the lower femur, and the upper tibia and fibula. They have also applied the experience gained in their anatomical studies to the examination of the normal knee-joint in the living subject and of a grafted double fracture of the tibia and fibula. They claim that the method should have wide application particularly, for example, for the precise location of pathological areas in bone and in the demonstration of articular displacements.

[The importance of this paper is that it gives a fair idea of the degree of radiographic definition which may be obtained by this method of examination.]

G. H. du Boulay.

Case of Reiter's Syndrome treated with Chloramphenicol. WHEATLEY, D. (1953). *Brit. J. vener. Dis.*, **29**, 162.

Side-Effects of "Irgapyrin". (Über Nebenwirkungen des Irgapyrins.) SCHNITZER, A. (1954). *Int. Arch. Allergy*, **5**, 47. 2 figs, 3 refs.

Dermatological Side-Effects of Irgapyrin. (Haut-Nebenerscheinungen nach Irgapyrin-medikationen.) JANSON, P. (1954). *Z. Haut- u. GeschlKr.*, **16**, 76.

"Butazolidin" in Joint Disease. (Butazolidin bei Arthrosen.) ZINN, W. (1954). *Schweiz. med. Wschr.*, **84**, 125. 3 figs, 18 refs.

So-called Periarthritis, Epicondylitis, and Styloiditis. (Die sogenannte Periarthritis, Epicondylitis und Styloiditis.) LANG, F. J., and SCHNEIDER, H. (1954). *Zbl. allg. Path. path. Anat.*, **91**, 342.

Succinate-Salicylate in Treatment of Arthritic Disorders. BRUSCH, C. A., KEENAN, G. F., SARGENT, A. F., DORGAN, J. A., and GRASSE, L. A. (1954). *Delaware St. med. J.*, **26**, 22. 2 figs, 4 refs.

Cortisone-like Action of Sodium Salicylate. (Sull'azione cortisone-simile del salicilato di sodio.) MURATORE, F., and RAMUNNI, M. (1954). *Reumatismo*, **6**, 111. 1 fig., bibl.

Assessment of the Response to Treatment in Rheumatic Diseases. (Bewertung des Therapieerfolges auf dem Gebiet der rheumatischen Erkrankungen.) HART, F. D. (1954). *Schweiz. med. Wschr.*, **84**, 265. 9 refs.

Radiological Studies of Bone Structure in Albers-Schönberg Disease. (Röntgenologische Studie zur Knochenstruktur bei der Albers-Schönbergschen Erkrankung.) LIESS, G., and DÖRFFEL, E. (1953). *Fortschr. Rontgenstr.*, **79**, 713. 11 figs, bibl.

Diagnostic Arthrography in Painful Conditions of the Shoulder. (L'artrografia opaca quale mezzo diagnostico nelle affezioni dolorose croniche della spalla.) CASTAGNOLI, M. (1954). *Reumatismo*, **6**, 30. 6 figs, 31 refs.

Pulmonary Silicosis with Rheumatism or the Syndrome of Colinet and Caplan. (Silicose pulmonaire et rhumatisme ou syndrome de Colinet-Caplan.) CLERENS, J. (1953). *Arch. belges Méd. soc.*, **11**, 336. 3 figs, 44 refs.

Morbidity among Underground Workers in a Ruhr Coal-Mine with special reference to the Rheumatic Diseases. (Das Krankheitsbild des Untertagebetriebes einer Zeche im Ruhrgebiet unter besonderer Berücksichtigung der rheumatischen Erkrankungen.) ARNOLD, R. (1954). *Z. Rheumaforsch.*, **13**, 38. 4 figs.

Rheumatism and Arthritis. Review of American and English Literature of Recent Years. (Tenth Rheumatism Review, Part 1.) ROBINSON, W. D., BOLAND, E. W., BUNIM, J. J., CRAIN, D. C., ENGLEMAN, D. P., GRAHAM, W., LOCKIE, L. M., MONTGOMERY, M. M., RAGAN, C., ROPES, M. W., ROSENBERG, E. F., and SMYTH, C. J. (1953). *Ann. intern. Med.*, **39**, 498.

Disk Syndrome

Dysphagia due to Cervical Spondylosis. BAUER, F. (1953). *J. Laryng.*, **67**, 615. 9 figs, 25 refs.

Cervical spondylosis is a more common cause of dysphagia than is generally recognized. After a short review of the literature, the author describes six cases of dysphagia due to cervical spondylosis in patients over the age of 50, and discusses the radiographs, which are reproduced. In the acute stage of the disease osteophytes on the anterior aspect of the cervical vertebral bodies give rise to oedema of the prevertebral tissues. This causes dysphagia from interference with the normal distension of the pharynx and oesophagus during the passage of a bolus. Later, parapharyngitis and paraoesophagitis result in fixation of the pharynx and gullet walls, preventing the normal gliding movement of the pharynx and interfering with the peristaltic wave of the pharyngeal constrictors. The recurrent laryngeal nerves may be involved in the inflammatory process, causing cord paralysis. The author emphasizes that oesophagoscopy is necessary to exclude the presence of carcinoma. Treatment consists in dilatation and a diet of soft foods, coupled with a reassurance of the patient that the condition is benign. The disease tends to spontaneous arrest. *H. D. Brown Kelly.*

Management of Sciatica by Vertebral Traction by means of Mechanical Table. NEUWIRTH, E. (1954). *Rheumatism*, **10**, 12. 4 figs, 6 refs.

Anterior Retromarginal Hernia of the Intervertebral Disk in the Lumbar and Lumbosacral Regions. (Les hernies discales rétro-marginales antérieures a la région lombaire et lombo-sacrée.) SÈZE, S. DE, DJIAN, A., and LÉVY-LEBHAR, J. P. (1953). *Rev. Rhum.*, **20**, 870. 8 figs.

Abolition of the Knee Jerk in Sciatica. (L'abolition du réflexe rotulien au cours de la sciatique.) LIÉVRE, J.-A., and BLOCH-MICHEL, H. (1953). *Rev. Rhum.*, **20**, 867. 2 refs.

Gout

Metabolic Studies in Gout with emphasis on the Role of Electrolytes in Acute Gouty Arthritis. LEVIN, M. H., RIVO, J. B., and BASSETT, S. H. (1953). *Amer. J. Med.*, **15**, 525. 6 figs, 21 refs.

It has been claimed that spontaneous attacks of gout are preceded by a diuresis of sodium and chloride, and that this is evidence of decreased activity of the adrenal cortex. The authors of this paper, who had previously failed to find diminished glucocorticoid excretion before attacks of gout, studied the electrolyte metabolism in two patients with gout at the Veterans Administration Center, Los Angeles. No evidence of diminished mineralocorticoid activity was found; "of the nine spontaneous gouty attacks studied none was associated with electrolyte or other changes indicative of decreased adrenal cortical function". Administration of mercurial drugs resulted in a marked sodium and chloride diuresis, but did not induce an attack of gout. The response to ACTH was normal, but after the drug was withdrawn attacks of gout were observed, although there was no evidence of abnormal "rebound" in the patients so far as mineralocorticoid function was concerned. Colchi-

cine administration was associated with some retention of sodium and chloride.

The general conclusion seems to be that spontaneous changes in sodium, chloride, and potassium balance occur in patients with gout as they do in normal subjects, and they are not related to the attacks of gout.

D. A. K. Black.

General Pathology

Pathology of Dupuytren's Contracture. WARREN, R. F. (1953). *Brit. J. plast. Surg.*, **6**, 224. 6 figs, 16 refs.

The pathology of Dupuytren's contracture was studied in 77 specimens of involved palmar fascia obtained from 65 patients under the care of the Department of Veterans' Affairs, Toronto. More than half the patients were under 50 years of age, and only two were female. Plantar fascia and other sites were sometimes affected. The palmar fibrosis was insidious in onset, starting as a thickening and nodularity of the palmar fascia and spreading to involve skin, interosseous fascia, tendon sheaths, and joint capsule. It was bilateral in forty cases. Subcutaneous fatty tissue was replaced by infiltration by two histologically distinct forms of fibrous tissue. Microscopically, remaining islets of fat were seen. The sweat glands were surrounded and there was considerable capillary vascularity. In the author's view the process is that of benign neoplasia. *W. Skyrme Rees.*

Urinary Steroid Excretion after Total Adrenalectomy. I. Levels of 17-Ketosteroids in Cancer Patients maintained on Varying Amounts of Cortisone Acetate and Glycyrrhizin. HUDSON, P. B., MITTELMAN, A., and MANN, P. (1953). *J. clin. Endocr.*, **13**, 1064. 3 figs, 8 refs.

Prompted by the work of Groen and others (*New Engl. J. Med.*, 1951, **244**, 471; *J. Clin. Invest.*, 1952, **31**, 87; *Abstracts of World Medicine*, 1951, **10**, 188, and 1952, **12**, 149) the authors have studied at the Institute of Cancer Research, Columbia University, New York, the effect of glycyrrhizinic acid in two post-menopausal women with cancer of the breast and one castrated man with prostatic cancer who had already undergone bilateral total adrenalectomy. After the operation the patients were satisfactorily maintained on 25 mg. cortisone acetate given twice daily by mouth. Later this dosage was reduced and supplemented with, and eventually replaced by, 4 g. daily ammoniated glycyrrhizin (*U.S.P.*), the liquorice extract with a deoxycortone-like action.

In all three patients the excretion of urinary 17-ketosteroids was reduced step-wise with each reduction of the dose of cortisone, the daily excretion being 3·6 mg. with 50 mg. cortisone daily, 1·99 to 2·5 mg. with 25 mg. daily, 1·3 mg. with 10 mg. daily, and 0·9 to 1·0 mg. with 5 mg. daily. These rates were unaffected by the addition of glycyrrhizin, and 17-ketosteroid excretion was virtually *nil* when the latter substance alone was given. The results do not entirely preclude the conversion of glycyrrhizin to steroidal substances, since atypical and unidentified chromogens were excreted in all patients and varied with the dose of cortisone. *Peter C. Williams.*

Serum Copper, Serum Iron, and Total Iron-Binding Capacity of Serum in Patients with Chronic Rheumatoid Arthritis. [In English.] BRENDSTRUP, P. (1953). *Acta med. scand.*, **146**, 384. 3 figs, 13 refs.

The serum iron and copper levels and the total iron-binding capacity of the serum were determined in patients with chronic rheumatoid arthritis at the Gigtsanatorium, Skelskør, Denmark. These levels were examined in relation to disease activity, those included in the "active" group being female patients with an erythrocyte sedimentation rate over 10, and male patients with a sedimentation rate over 6 mm./hr [presumably by the Westergren method], unless these values were due to complicating disease, together with patients showing fever, anaemia, or particularly active joint lesions. Analysis was also made according to sex and to joint mobility, the latter being a numerical index obtained by calculating the sum of the mobilities of all joints of the extremities except the fingers and toes, according to Kalbak's method, and expressing this as a fraction of the normal.

Serum iron showed a mean level of 68·6 μg./100 ml. in 85 active cases, there being no sex difference, as against 98 μg./100 ml. in 37 inactive cases, in which, as expected, women showed figures somewhat lower than the men, but both showed values above their respective "active" counterparts. The serum copper level was much higher in the "active" group (188 μg./100 ml. in 88 patients) than in the "inactive" group (132 μg./100 ml. in 45 patients). No sex difference was apparent in either group. Analysis according to duration of illness showed little difference between the inactive and active groups, but as followed from the method of selection the erythrocyte sedimentation rate was higher and the haemoglobin values and mobility index considerably lower in the active group. The same tendency was seen for joint mobility as for activity, the serum iron level being lower and the copper level higher in the least mobile patients [no standard deviations are given]. The total iron-binding capacity, which was measured in nine patients with active rheumatoid arthritis and a high erythrocyte sedimentation rate, was found to be reduced below normal in all of them to a mean level of 183 μg./100 ml. The reduction from normal was, however, not as great as that of the serum iron levels. Three patients (two with disseminated lupus erythematosus and one with Reiter's syndrome) were treated with ACTH for periods ranging from 6 days to 3 weeks. Although the figures are incomplete, the serum iron values and the total iron binding capacity appeared to rise, and the serum copper level in one case was reduced.

The author concludes that the determination of the serum iron and serum copper values has no practical advantage over the determination of the erythrocyte sedimentation rate as a measure of disease activity.

E. G. L. Bywaters.

Effect of ACTH on the Eosinophil Count in Peripheral Blood and Bone Marrow. ROOT, S. W., and ANDREWS, G. A. (1953). *Amer. J. med. Sci.*, **226**, 304. 11 refs.

At the Oak Ridge Institute of Nuclear Studies, Tennessee, an attempt was made to determine the cause of

the fall in the number of circulating eosinophil granulocytes which normally occurs after the administration of ACTH (corticotrophin).

Specimens of blood and bone marrow were obtained from twelve subjects before and after the intravenous or intramuscular administration of 25 mg. ACTH, in each case, the intravenous dose being infused over a period of 7 hrs. While there was the usual fall in the eosinophil count in the peripheral blood (which was studied at 1- or 2-hr intervals) there was no significant change in the number of eosinophils in the marrow (studied 4 hours after the intramuscular injection and on conclusion of the intravenous infusion of ACTH) at any stage in their development, suggesting that ACTH caused no interference with the rate of their production. Nor was any change observed in the number of mature eosinophils in the marrow or evidence of eosinophil destruction there.

It is concluded that the bone marrow does not play an important role in the phenomenon of eosinopenia after the administration of ACTH. *G. S. Crockett.*

Osteoblasts and Osteoclasts in Bone Marrow Aspiration. Previously Undescribed Cell Findings in Paget's Disease (Osteitis Deformans). RUBINSTEIN, M. A., SMELIN, A., and FREEDMAN, A. L. (1953). *Arch. intern. Med.*, **92**, 684. 10 figs, 20 refs.

Two new types of cell found in bone marrow aspirated from patients with osteitis deformans are here described. In the investigation of eight cases of osteitis deformans at the Montefiore Hospital, New York, histological examination of a smear of bone marrow aspirated from the iliac bone involved revealed large mononuclear cells and giant multinucleated syncytial forms.

The individual mononuclear cell is ovoid, measures 25 to 50μ at its greatest diameter, and has hazy cytoplasmic borders. The nucleus is round, with a diameter of 12 to 16μ, is located eccentrically, and frequently appears to have been partially excluded from the cytoplasm. These cells may occur singly or in clumps of two or three, the total number varying inversely with the haematopoietic activity of the marrow. They are not found in bones in which there is no radiological evidence of Paget's disease.

The syncytial cell forms may be over 200μ in diameter and contains as many as 100 nuclei, which are of uniform size and are distributed haphazardly throughout the syncytium. These cells were found in three of the eight cases. It is presumed that the mononuclear cells correspond to osteoblasts and the multinucleate forms to osteoclasts.

The authors suggest that the finding of these cells may be of help in the diagnosis of Paget's disease.

[The article is well illustrated.] *E. G. Rees.*

Diagnostic Tests for Acute Rheumatism. (Maladie de Bouillaud. Les tests d'identification.) LUTEMBACHER, R. (1954). *Presse méd.*, **62**, 205.

Bacteriologic Aspects of Rheumatic Disease. SEVERENS, J. M. (1954). *Neb. St. med. J.*, **39**, 52.

Picture of the Bone Marrow in the Rheumatic Disease. (Obraz szpiku w chorobie gośćcowej.) MACKIEWICZ, S. (1953). *Pol. Tyg. lek.*, **8**, 1753. 3 figs, 20 refs.

Histochemical Studies on Cartilage and Bone. III. Osteogenesis Imperfecta. FOLLIS, R. H. (1953). *Bull. Johns Hopk. Hosp.*, **93**, 386. 17 refs.

Researches into the Rate of Sedimentation of Erythrocytes in Synovial Fluid. (Ricerche sulla velocita di sedimentazione dei globuli rossi nel liquido sinoviale.) CARTESEGNA, F., and DANEO, V. (1954). *Reumatismo*, **6**, 128. 14 refs.

A Study of the Adrenocortical Lipids in Various Experimental Conditions. I. The Action of Artificial Pyrexia. (Studio dei lipidi corticosurrenalici in diverse condizioni sperimentali. I. Azione della piressa artificiale.) SUMMA, C., and VOLPICELLI, M. (1953). *Reumatismo*, **5**, 358. 6 figs, bibl.

II. Action of Colchicine. (II. Azione della colchicina.) LUCHERINI, T., SUMMA, C., and VOLPICELLI, M. (1954). *Reumatismo*, **6**, 12. 4 figs, 31 refs.

Agglutination of Sensitized Erythrocytes as a Serological Diagnostic Test for Rheumatoid Arthritis. I. Investigation of Methods. (Über die zur serologischen Diagnose der chronischen Polyarthritis angewandte Agglutinationsreaktion mit sensibilisierten Erythrocyten. I. Methodische Untersuchungen.) DICKGIESSER, F., and HARTER, F. (1953). *Z. ges. exp. Med.*, **122**, 221. 28 refs.

Studies on Agglutination in Rheumatoid Arthritis. I. Attempts to Purify the Factor causing Agglutination of Sensitized Erythrocytes. WAGER, O., and ALAMERI, E. (1953). *Ann. Med. exp. Biol. Fenn.*, **31**, 361. 3 figs, 15 refs.

ACTH, Cortisone, and Other Steroids

ACTH in Reiter's Syndrome; Four Cases with Review of the Literature. LARSON, E., and ZOECKLER, S. J. (1953). *Amer. J. Med.*, **14**, 307.

Four cases of this syndrome are discussed, and as the condition is self-limiting, the authors believe that the primary objectives of treatment should be the shortening of the illness and the prevention of permanent disability. In this respect, antibiotics, sulpha drugs, antihistamines, and TAB failed, whereas ACTH gave dramatic relief from pain, stimulated appetite, and permitted vigorous physio-therapeutic measures. The literature is fully reviewed. *J. R. Hudson.*

Intra-Articular Hydrocortisone in the Treatment of Arthritis. HOLLANDER, J. L. (1953). *Ann. intern. Med.*, **39**, 735. 7 figs, 7 refs.

Intra-articular injection of hydrocortisone was tried in the treatment of 852 patients with arthritis at the Hospital of the University of Pennsylvania, Philadelphia, a total of 8,693 injections being given into inflamed joints, bursae, and tendon sheaths. Treatment was considered to be successful if there was unequivocal improvement in symptoms and signs in the affected joint for a minimum of three days.

The best results were obtained from injection into the knee-joint, there being only 6 per cent. of failures in this group. In contrast, 52 per cent. of the injections into the hip-joint failed to give relief, this being attributed largely to technical difficulty. In acute subdeltoid bursitis the failure rate was 21 per cent. and in the chronic form it was 51 per cent. The author emphasizes the importance of injecting the hydrocortisone into the synovial space.

Of 547 patients followed up for at least one year, 106 obtained lasting relief of symptoms and signs of local inflammation for at least 12 months. This number included many patients with gout, traumatic arthritis, bursitis, and tenosynovitis, the exacerbations of which are, of course, self-limiting; it also included, however, 31 patients with osteo-arthritis and fourteen with rheumatoid arthritis. Although relief was temporary in 296 patients (54 per cent.) it was maintained by repeated injection for more than a year. Little or no benefit was obtained by eighty patients. The remaining 65 patients were lost to the long-term study.

Of 8,693 injections only 199 (2·3 per cent.) were followed by an untoward reaction, which, in the majority of cases, consisted in a temporary exacerbation of the joint inflammation, lasting a few hours to a few days, and often followed by improvement over the pre-treatment state. Other untoward reactions included local or general weakness, and hives at the site of injection. In only two instances did infection of the joint occur, and this was successfully treated with penicillin. *C. E. Quin.*

Effect of ACTH in Polyphloretin Phosphate Solution (Clinical and Metabolic Studies). [In English.] FISCHER, F., FRIIS-HANSEN, B., GEORG, J., HASTRUP, B., KALBAK, K., SPRECHLER, M., WARMING-LARSEN, A., and WULFF, H. (1953). *Acta endocr.* (*Kbh.*), **13**, 293. 9 figs, 19 refs.

The authors have noticed a pronounced tendency among patients treated with ACTH (corticotrophin) in polyphloretin phosphate solutions to develop oedema, and have studied the problem, particularly in regard to electrolyte and fluid metabolism. Investigations were carried out at the Rigshospitalet, Copenhagen, over a period of 6 weeks on a young male patient suffering from anhydrous spondylitis associated with rheumatoid arthritis, who was treated successively with polyphloretin phosphate alone (2 ml. daily for one week), ACTH alone (four doses of 20 units daily for one week), and ACTH dissolved in polyphloretin phosphate (one dose of 20 units daily for 2 weeks), with intervening control periods in which injections of saline were given. Nitrogen and electrolyte balances were determined throughout, but no significant difference was found between the period in which ACTH was given alone and that in which the composite dose was given; the blood chemistry and the urinary steroid output were also similar during the two periods. Water distribution was studied by the use of heavy water (Schloerb and others, *J. clin. Invest.*, 1950, **29**, 1296) and by the thiosulphate technique (Cardoza and Edelman, *J. clin. Invest.*, 1952, **31**, 280) and it was shown that during treatment with ACTH the extracellular space expands at the expense of the intracellular; but again no qualitative differences were observed between the two periods mentioned. Nor was the clinical state of the patient different, subjectively or objectively, whether the ACTH was given alone or with polyphloretin phosphate. Thus it would appear that polyphloretin phosphate has no metabolic or clinical activity *per se*, and that it does not alter qualitatively the effect of ACTH, but prolongs and intensifies its action, one dose of ACTH in polyphloretin phosphate being equivalent in this case to four doses of ACTH alone. *Nancy Gough.*

Hydrocortone and Soft-Tissue Lesions. CYRIAX, J., and TROISIER, O. (1953). *Brit. med. J.*, **2**, 966. 1 ref.

The authors of this paper advocate the local injection of "hydrocortone" (Kendall's Compound F, 17-hydroxycorticosterone) for the treatment of chronic inflammation of fibrous tissues resulting from trauma. [No case reports are quoted, however, and there are no references to the literature.] The authors have not found it helpful in the treatment of freezing arthritis (*sic*) of the shoulder, and consider that the indications for manipulation in such cases remain unaltered. They report that tennis elbow and other tendinous lesions respond particularly well to local injections of hydrocortone (hydrocortisone). *W. S. C. Copeman.*

Effect of topically administered Cortisone on experimentally induced Contact Dermatitis in Human Beings. [In English.] SCHWARTZ, M. (1953). *Acta allerg.* (*Kbh.*), **6**, 134. 15 refs.

In view of the good results obtained with cortisone in some eye conditions and in certain types of lupus erythematosus, the effect of topically administered cortisone on experimentally-induced contact dermatitis was investigated at the City Infirmary Hospital (Washington University School of Medicine), St. Louis.

For 9 consecutive days, 375 mg. cortisone ointment was rubbed daily into an area of 40 sq. cm. on the left forearm of eleven subjects who had previously been sensitized to 2:4-dinitrochlorobenzene (DNCB); the right forearm in each case served as a control, ointment base only being applied. On the tenth day the skin was challenged with DNCB. Subsequently six patients continued inunction of cortisone daily for 8 days to both arms, the remaining five patients using ointment base only. The cortisone ointment in no way altered the development or course of the contact dermatitis. *A. W. Frankland.*

Local Use of Hydrocortisone Acetate: a Preliminary Report. ROBINSON, R. C. V. (1953). *Bull. Johns Hopk. Hosp.*, **93**, 147. 5 refs.

Forty-two patients with atopic dermatitis, pruritus ani, pruritus vulvae, or discoid lupus erythematosus, were treated with topical applications of an ointment containing 2·5 per cent. hydrocortisone acetate. Twenty of 28 patients with atopic dermatitis showed definite improvement within 24 hrs. All patients had exacerbations when applications were discontinued. Five of eight patients with pruritus vulvae and one of three with pruritus ani improved as long as the ointment was kept applied but sustained flare-ups on withdrawal.

The results in discoid lupus erythematosus in this series

are such that further study is indicated, since other investigators do not agree as to its value.—[*Author's summary.*]

ACTH immediately after Operation for Arachnoiditis affecting the Optic Chiasma. (L'ACTH dans les suites opératoires immédiates des arachnoïdites opto-chiasmatiques.) FEREY, D. (1953). *Presse méd.*, **61**, 410. 3 figs.

Considerable visual improvement was seen in two cases after the administration of ACTH and cortisone: 4 days after operation in one case, and immediately after in the second. (ACTH 12·5 mg. four times daily for 20 days; cortisone 100 mg. once, then 25 mg. for 16 days.)

M. H. T. Yuille.

Treatment of Eczema with Cortisone Ointment. VOLLMER, H. (1953). *Arch. Derm. Syph.* (*Chicago*), **68**, 525. 15 refs.

Atopic dermatitis in 35 children was treated with cortisone ointments containing between 3 and 25 mg. cortisone per gram of various ointment bases. Results from 68 treatment periods of at least one week's duration were observed. Eczema was slightly improved in 31 (45·6 per cent.), was unimproved in 34 (50·0 per cent.) and became worse in three (4·4 per cent.). Relapses followed improvement in almost all cases after cessation of treatment.

Eosinophil responses to 21 treatments with topically applied cortisone in fifteen patients indicated little if any absorption of cortisone into the circulation. It is concluded that local absorption was also insufficient in the majority of cases. With the cortisone ointments used, an effective concentration of cortisone was probably not reached in the affected skin layers.

The therapeutic effect of cortisone ointment in eczema does not exceed the results obtained with conventional dermatologic treatment.—[*Author's summary.*]

Evaluation of Treatment of Ragweed-Sensitive Patients with Adrenocorticotropic Hormone in Gelatin. ROY, J., COOKE, R. A., and SHERMAN, W. B. (1953). *J. Allergy*, **24**, 506. 2 refs.

At the Institute of Allergy, Roosevelt Hospital, New York, twenty patients with ragweed hay fever, with or without asthma, were treated during the ragweed season with 40 units ACTH gel daily for periods varying from 2 to 19 days. There was marked improvement in all patients within 48 hrs, and the majority were symptom-free after four or five injections. Two patients with hay fever, who had become free of symptoms after two and three injections respectively during the height of the season, remained free during the remainder of the ragweed season without any further treatment.

H. Herxheimer.

Corticosteroids and Antidiuretic Substance in Nephrotic Children. GALÁN, E., PÉREZ-STABLE, M., GARCÍA FAEZ, O., UNANUE, E., GARCÍA, O., LABOURDETTE, J. M., and ALFONSO, G. (1953). *Pediatrics*, **12**, 233. 6 figs, bibl.

In order to study the effects of corticosteroids and antidiuretic substances on diuresis in nephrotic children the presence and distribution of these substances was investigated at the Children's Hospital, Havana, in four such children, two of whom were free from signs of glomerular involvement. One other child suffering from acute haemorrhagic glomerulonephritis without the nephrotic syndrome was included in the series so as to detect any possible difference that might be due to the nephrotic syndrome. Three further children recovering from other diseases and without any detectable sign of renal dysfunction served as controls. All five children with nephropathies had marked impairment of renal function as judged by the results of clearance tests. Clinical records included daily assessment of the physical status (oedema, weight, diuresis, blood pressure), diet, and liquid intake. The diet was calculated to contain 54 g. protein, 0·84 g. salt, 1,800 ml. water, and to supply about 1,000 to 1,250 Cal. per day. Determinations of the urinary volume, urinary protein content, and excretion levels of electrolytes and steroids were carried out daily, those of the blood chemical constituents and level of antidiuretic substance twice weekly, and clearance tests and urinary deposits were studied every 2 weeks for periods up to 2 months.

The results are shown in charts, tables, and graphs. Nephrotic children showed a low excretion of steroids during periods of spontaneous increase of diuresis and reduction of oedema, whereas in the child with glomerulonephritis there was increased steroid excretion during a similar event. A similar occurrence took place during the administration of ACTH (corticotrophin) or of concentrated human plasma albumin, but nothing similar was seen in the control patients. The urinary excretion of steroids in both the nephrotic and normal children was in relation to the tubular reabsorption function, as shown by the results of inulin and thiosulphate clearance tests, but in nephrotic children, after stimulation of the adrenal cortex by administration of ACTH, no proportional increase in urinary steroid excretion occurred, whereas the plasma steroid level increased during that period (except in one case). Plasma steroid concentration was influenced by adrenal and renal function and by the extent of diffusability of steroids into the interstitial fluid. There was some evidence of retention of steroids in ascitic fluid during oliguric periods. An antidiuretic substance was present in the globulin fraction of the plasma of nephrotic children, but it was not found in ascitic fluid, plasma filtrate, or in the plasma albumin fraction, as proved by the effect of intraperitoneal injection of these extracts into rats.

L. H. Worth.

Studies in Nephrosis: Chemical Corticoids, Salt-Retaining Factor, and Effect of ACTH. MCCALL, M. F., and SINGER, B. (1953). *J. clin. Endocr.*, **13**, 1157. 4 figs, 11 refs.

The accumulation of oedematous fluid in nephrotic patients is probably due to a renal glomerular-tubular imbalance, of which a possible cause may be an excess in the secretion of adrenocortical salt-retaining hormone (electrocortin). This can be measured in terms of deoxycortone acetate by determining the sodium reten-

tion produced in adrenalectomized rats injected with radio-active sodium (^{24}Na). The method is applicable to extracts of urine.

At the Children's Memorial and Royal Victoria Hospitals (McGill University), Montreal, fourteen oedematous children with uncomplicated nephrosis were studied. Their urinary excretion of corticoids (chemically determined by formaldehyde formation during oxidation with periodic acid) was normal, but was increased during treatment with ACTH (corticotrophin). When the excretion level reached 1 mg. daily or more (normal values 0·03 to 0·3 mg.) there was complete diuresis and remission. A second course of treatment with ACTH produced a greater effect, and diuresis was induced in three of the four cases which had not responded adequately to the first course. This relation between the level of corticoid excretion and diuresis was also shown to hold in two nephrotic patients in whom the excretion was increased by intercurrent infection; severe infection, however, produced a large increase in excretion and no diuresis. All but one of the nine patients examined during the accumulation of oedema showed an abnormally high urinary excretion of electrocortin, which was not evident in the same patients when their oedema was stabilized or was being reduced by treatment with ACTH. Symptoms recurred in 1 to 9 months in five patients, but two had no recurrence in periods of 14 and 24 months respectively. The time of recurrence bore no relation to the speed of the initial response.

The normal rate of corticoid excretion which was seen in these patients may have been due to an imbalance in the various excretion products as measured by the chemical method, and increased excretion of electrocortin may be accompanied by a decrease in that of carbohydrate-active steroids. Electrocortin secretion is not usually thought to be controlled by ACTH, and it may be that treatment with this substance corrects the imbalance by increasing secretion of the other adrenal steroids. It was noticeable that diuresis usually occurred after treatment was stopped, when total corticoid excretion fell to very low values. *Peter C. Williams.*

Relationship between the Actions of Adrenocortical Steroids and Adrenomedullary Hormones in the Production of Eosinopenia. HENRY, W. L., OLINER, L., and RAMEY, E. R. (1953). *Amer. J. Physiol.*, **174**, 455. 1 fig., 11 refs.

In this paper the authors report from the University and Michael Reese Hospital, Chicago, their findings on the effects of cortisone and adrenaline on the level of circulating eosinophils in intact and adrenalectomized dogs, in one patient whose adrenal glands had been removed, and in another patient with Addison's disease. Cortisone in a dose of 1 to 3 mg./kg. body weight intramuscularly produced after 4 hrs a significant fall in the number of circulating eosinophils in the intact animals, but not in those which had been adrenalectomized. In these latter the injection of 0·3 mg. adrenaline 4 hrs after the cortisone resulted in a significant reduction of eosinophils in a further 2 hrs, whereas adrenaline without preceding cortisone caused a slight rise in eosinophil count. Similarly, when the patients, who were both being maintained on cortisone, were given 0·3 mg. of adrenaline subcutaneously, the eosinophil count fell by over 60 per cent by the end of 4 hrs.

The authors cite other work in agreement with these findings and conclude that adrenaline and the C-11 oxysteroids have a synergic action in producing eosinopenia. They also suggest that in the intact animal adrenaline may also produce an increased liberation of ACTH (corticotrophin) which may contribute towards the reduction in the number of eosinophils. *G. A. Smart.*

Cortisone and ACTH in Treatment of Non-Rheumatic Conditions. ABER, G. M., CHANDLER, G. N., and HARTFALL, S. J. (1954). *Brit. med. J.*, **1**, 1. 3 figs, 13 refs.

The effect of cortisone and ACTH in non-rheumatic diseases has been studied in 43 patients.

Fourteen patients with disorders of the blood have been observed. A favourable response occurred in three children with acute acquired haemolytic anaemia, and in thrombocytopenic purpura apparent clinical benefit resulted in the two patients treated. No effects were produced in aplastic anaemia, though one patient with acute agranulocytosis from thiouracil made a good response. The effect of ACTH in leukaemia was at best temporary. This small experience suggests that, apart from acquired haemolytic anaemia and some cases of purpura, cortisone and ACTH have little place in the treatment of blood disorders.

Sixteen patients with disorders of endocrine function have been studied. Of nine patients with exophthalmic ophthalmoplegia, only three responded well, the best results being obtained with ACTH in those examples of recent onset or rapid progression. Three patients with Simmonds's disease have made a dramatic and sustained improvement on ACTH. Two patients showing the virilizing effects of adrenal hyperplasia have been treated by adrenalectomy and cortisone: in neither did the results obtained appear to justify the risks involved. 17-Ketosteroid excretion was controlled in two pseudohermaphrodites by the use of cortisone.

The beneficial effect of cortisone and ACTH in asthma has been confirmed. The use of ACTH by intravenous drip and of cortisone by inhalation usually brought prompt improvement and was an important economy in prescribing. In two patients with nephrosis a considerable diuresis attended treatment, and in one of them the remission obtained has lasted more than a year. There is no evidence that ACTH influences portal hypertension accompanying cirrhosis, though apparent clinical benefit occurred in one patient.—[*Authors' summary.*]

Histopathologic Changes in the Adrenal and Anterior Pituitary in Patients treated with Cortisone: Preliminary Impressions. BENNETT, W. A. (1953). *Proc. Mayo Clin.*, **28**, 658. 4 refs.

The author has studied the adrenal glands of 190 patients who died at the Mayo Clinic of various diseases and who had received various doses of cortisone or

related hormones over periods of not less than 5 days ending up to 4½ months before death. In many cases where a total of more than 450 mg. cortisone had been given the weight of the adrenal glands was less than normal (6 to 8 g.) and deficient in lipids as shown histologically in sections stained with Sudan IV. These changes were, however, reversible, and normal glands were found in most cases where administration of cortisone had been discontinued *more than 6 weeks* before death. The whole pattern of adrenal changes appeared to be subject to considerable individual variation.

Mention is also made of unpublished studies by Kilby on the anterior lobe of the pituitary in 77 of the same cases. The basophil cells were affected to a greater or less extent in all cases. The earliest change was clumping of the granules, which later disappeared, with hyalinization and vacuolization of the cytoplasm. The severity of these changes could be correlated with the amount of hormone given, the duration of treatment, and the lapse of time between cessation of treatment and death. Corticotrophin produced earlier and more severe changes than did cortisone. *D. G. Adamson.*

Clinical Aspects of Suppression of Adrenal Cortical Function after Use of Cortisone. SALASSA, R. M., KEATING, F. R., and SPRAGUE, R. G. (1953). *Proc. Mayo Clin.*, **28**, 662. 8 refs.

Since cortisone can suppress the function of the adrenal cortex, and since this effect may persist for some time after administration of the drug is stopped, there is a danger of acute adrenal insufficiency occurring after the stress of an operation in patients who have previously received cortisone therapy. The exact duration of the suppressive effect after the withdrawal of cortisone is unknown, but on the basis of available evidence the authors suggest that any patient who has received cortisone in significant amounts within 3 to 6 months of an operation should receive prophylactic treatment and that "any patient who has had extensive hypercortisonism within 1 to 1½ years of a proposed operation should, perhaps, be treated as though liable to acute adrenal insufficiency".

From experience gained at the Mayo Clinic in the operative and post-operative care of patients with Addison's disease the authors suggest that prophylactic treatment should consist in the administration of 200 mg. cortisone intramuscularly 48, 24, and 1 or 2 hrs before operation. Oral administration is not recommended. The administration of cortisone should usually be continued for 3 or 4 days post-operatively in reduced dosage. All patients who have received cortisone therapy before operation, whether or not they have been given prophylactic treatment, should be watched carefully during the first 24 hrs since this is the danger period. If acute adrenal insufficiency does develop the authors recommend the intravenous infusion of isotonic saline or 5 per cent. glucose solution combined with the intravenous injection of cortisone or hydrocortisone if suitable preparations are available. Otherwise, large quantities of aqueous adrenal extract should be given both intravenously and intramuscularly, while noradrenaline in doses of 4 mg. can with advantage be added to the saline; although no immediate effect can be expected, 200 mg. of cortisone should be injected intramuscularly or given by mouth if nausea and vomiting are absent. *D. G. Adamson.*

17-Hydroxycorticosterone Content of Human Ascitic Fluid. COPE, C. L., and HURLOCK, B. (1953). *Brit. med. J.*, **2**, 753. 1 fig., 19 refs.

The difficulty experienced in estimating the small quantities of biologically active steroids present in the peripheral blood prompted the authors to study the steroid content of human ascitic fluid, this being obtainable in large quantities. Samples of 3 to 7 litres were obtained from "suitable patients", extracted with chloroform, and the extract then taken up successively in acetone (with magnesium chloride) and ethanol, re-dissolved in chloroform, and evaporated to dryness by a stream of nitrogen.

Extracts equivalent to 1,500 ml. ascitic fluid were dissolved in propylene glycol and injected subcutaneously into adrenalectomized mice, and the fall in eosinophil count determined after 4 and 6 hrs, the greater fall being regarded as the significant value. The activity of the fluid was expressed in terms of the equivalent cortisone content, a calibration curve having been prepared by injecting cortisone acetate in various doses into adrenalectomized mice under identical conditions.

Of the ten samples of ascitic fluid examined in this way by the authors, five showed activity equivalent to more than 1·5 μg. cortisone per 100 ml. Three others gave equivocal results, the activity of samples removed from the same patient at different times varying, while the remaining two samples showed no activity at all. Equivalent activity did not exceed 5 μg./100 ml. in any sample. Analysis of four of the extracts demonstrated the presence of a substance behaving like 17-hydroxycorticosterone, as shown by:

(1) its rate of flow on paper chromatography;
(2) its ability to reduce the blue tetrazolium reagent; and
(3) its absorption of ultraviolet light at 240 mμ.

It was possible to estimate the quantity of 17-hydroxycorticosterone chemically in one extract. Cortisone was detected as a faint trace in only one of the extracts.

The authors tentatively suggest that the hormone content of ascitic fluid may be indicative of the content of extracellular fluid in general, and that their inability to demonstrate any hormonal activity in two of the samples may indicate that under some conditions adrenal cortical hormone diffuses with difficulty from the blood into the extracellular fluid. This might possibly explain the response of the tissues and joints in rheumatoid arthritis to cortisone or 17-hydroxycorticosterone therapy, although adrenal cortical function appears to be normal in this disease. *Robert de Mowbray.*